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(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 90 Green Meadow Drive, Tewksbury, MA 01876 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). AGOSTINO, Michael, J.; 26 Wolcott Avenue, Andover, MA 01810 (US).

(74) Agent: SPRUNGER, Suzanne, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).

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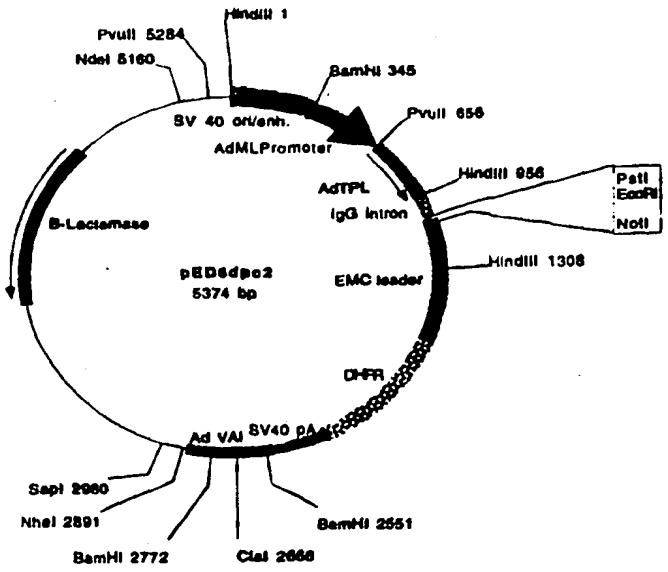
(57) Abstract

Polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

This application is a continuation-in-part of Ser. No. 60/XXX,XXX (converted to a provisional application from non-provisional application Ser. No. 08/788,789), filed January 24, 1997, which is incorporated by reference herein.

FIELD OF THE INVENTION

The present invention provides novel polynucleotides and proteins encoded by such polynucleotides, along with therapeutic, diagnostic and research utilities for these polynucleotides and proteins.

BACKGROUND OF THE INVENTION

Technology aimed at the discovery of protein factors (including e.g., cytokines, such as lymphokines, interferons, CSFs and interleukins) has matured rapidly over the past decade. The now routine hybridization cloning and expression cloning techniques clone novel polynucleotides "directly" in the sense that they rely on information directly related to the discovered protein (i.e., partial DNA/amino acid sequence of the protein in the case of hybridization cloning; activity of the protein in the case of expression cloning). More recent "indirect" cloning techniques such as signal sequence cloning, which isolates DNA sequences based on the presence of a now well-recognized secretory leader sequence motif, as well as various PCR-based or low stringency hybridization cloning techniques, have advanced the state of the art by making available large numbers of DNA/amino acid sequences for proteins that are known to have biological activity by virtue of their secreted nature in the case of leader sequence cloning, or by virtue of the cell or tissue source in the case of PCR-based techniques. It is to these proteins and the polynucleotides encoding them that the present invention is directed.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 506 to nucleotide 643;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 471 to nucleotide 765;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AA35_2 deposited under accession number ATCC 98303;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AA35_2 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 506 to nucleotide 643; the nucleotide sequence of SEQ ID NO:1 from nucleotide 471 to nucleotide 765; the nucleotide sequence of the full-length protein coding sequence of clone AA35_2 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone AA35_2 deposited

under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 32.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:1.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 32;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:2 or the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 32.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 71 to nucleotide 736;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 113 to nucleotide 736;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 343;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AM42_3 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AM42_3 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:3 from nucleotide 71 to nucleotide 736; the nucleotide sequence of SEQ ID NO:3 from nucleotide 113 to nucleotide 736; the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 343; the nucleotide sequence of the full-length protein coding sequence of clone AM42_3 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone AM42_3 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 91.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:3.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 91;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:4 or the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 91.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 55 to nucleotide 423;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG137_7 deposited under accession number ATCC 98303;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG137_7 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:5 from nucleotide 55 to nucleotide 423; the nucleotide sequence of the full-length

protein coding sequence of clone BG137_7 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone BG137_7 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6 from amino acid 62 to amino acid 123.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:5.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 62 to amino acid 123;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:6 or the amino acid sequence of SEQ ID NO:6 from amino acid 62 to amino acid 123.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 186 to nucleotide 2030;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 873 to nucleotide 2030;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 802 to nucleotide 1173;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CH699_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CH699_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:7 from nucleotide 186 to nucleotide 2030; the nucleotide sequence of SEQ ID NO:7 from nucleotide 873 to nucleotide 2030; the nucleotide sequence of SEQ ID NO:7 from nucleotide 802 to nucleotide 1173; the nucleotide sequence of the full-length protein coding sequence of clone CH699_1 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone CH699_1 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8 from amino acid 218 to amino acid 329.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:7.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 218 to amino acid 329;

(c) fragments of the amino acid sequence of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:8 or the amino acid sequence of SEQ ID NO:8 from amino acid 218 to amino acid 329.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 111 to nucleotide 677;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 156 to nucleotide 677;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CO851_1 deposited under accession number ATCC 98303;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CO851_1 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:11;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:11 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:10 from nucleotide 111 to nucleotide 677; the nucleotide sequence of SEQ ID NO:10 from nucleotide 156 to nucleotide 677; the nucleotide sequence of the full-length protein coding sequence of clone CO851_1 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone CO851_1 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein, comprising the amino acid sequence of SEQ ID NO:11 from amino acid 120 to amino acid 189.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:10, SEQ ID NO:9 or SEQ ID NO:12 .

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:11;

(b) the amino acid sequence of SEQ ID NO:11 from amino acid 120 to amino acid 189;

(c) fragments of the amino acid sequence of SEQ ID NO:11; and

(d) the amino acid sequence encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:11 or the amino acid sequence of SEQ ID NO:11 from amino acid 120 to amino acid 189.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 123 to nucleotide 755;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 279 to nucleotide 755;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 631;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CP111_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CP111_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:13 from nucleotide 123 to nucleotide 755; the nucleotide sequence of SEQ ID NO:13 from nucleotide 279 to nucleotide 755; the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 631; the nucleotide sequence of the full-length protein coding sequence of clone CP111_1 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone CP111_1 deposited

under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 171.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:13.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 171;

(c) fragments of the amino acid sequence of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:14 or the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 171.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 214 to nucleotide 2760;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 406 to nucleotide 2760;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 2011 to nucleotide 2565;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CS278_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CS278_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:15 from nucleotide 214 to nucleotide 2760; the nucleotide sequence of SEQ ID NO:15 from nucleotide 406 to nucleotide 2760; the nucleotide sequence of SEQ ID NO:15 from nucleotide 2011 to nucleotide 2565; the nucleotide sequence of the full-length protein coding sequence of clone CS278_1 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone CS278_1 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16 from amino acid 596 to amino acid 784.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:15.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 596 to amino acid 784;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:16 or the amino acid sequence of SEQ ID NO:16 from amino acid 596 to amino acid 784.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 901 to nucleotide 1074;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 970 to nucleotide 1074;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 626 to nucleotide 1147;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DF968_3 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DF968_3 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:17 from nucleotide 901 to nucleotide 1074; the nucleotide sequence of SEQ ID NO:17 from nucleotide 970 to nucleotide 1074; the nucleotide sequence of SEQ ID NO:17 from nucleotide 626 to nucleotide 1147; the nucleotide sequence of the full-length protein coding sequence of clone DF968_3 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone DF968_3 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:17.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) fragments of the amino acid sequence of SEQ ID NO:18; and

(c) the amino acid sequence encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:18.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 560 to nucleotide 820;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DN1120_2 deposited under accession number ATCC 98303;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DN1120_2 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:19 from nucleotide 560 to nucleotide 820; the nucleotide sequence of the full-length protein coding sequence of clone DN1120_2 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone DN1120_2 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303. In yet other preferred embodiments, the present invention provides a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 61.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:19.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 61;

(c) fragments of the amino acid sequence of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:20 or the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 61.

In one embodiment, the present invention provides a composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 649 to nucleotide 786;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 736 to nucleotide 786;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 525 to nucleotide 787;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DO589_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DO589_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

Preferably, such polynucleotide comprises the nucleotide sequence of SEQ ID NO:21 from nucleotide 649 to nucleotide 786; the nucleotide sequence of SEQ ID NO:21 from nucleotide 736 to nucleotide 786; the nucleotide sequence of SEQ ID NO:21 from nucleotide 525 to nucleotide 787; the nucleotide sequence of the full-length protein coding sequence of clone DO589_1 deposited under accession number ATCC 98303; or the nucleotide sequence of the mature protein coding sequence of clone DO589_1 deposited under accession number ATCC 98303. In other preferred embodiments, the polynucleotide encodes the full-length or mature protein encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303.

Other embodiments provide the gene corresponding to the cDNA sequence of SEQ ID NO:21.

In other embodiments, the present invention provides a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

(b) fragments of the amino acid sequence of SEQ ID NO:22; and

(c) the amino acid sequence encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins. Preferably such protein comprises the amino acid sequence of SEQ ID NO:22.

In certain preferred embodiments, the polynucleotide is operably linked to an expression control sequence. The invention also provides a host cell, including bacterial, yeast, insect and mammalian cells, transformed with such polynucleotide compositions. Also provided by the present invention are organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein.

Processes are also provided for producing a protein, which comprise:

(a) growing a culture of the host cell transformed with such polynucleotide compositions in a suitable culture medium; and

(b) purifying the protein from the culture.

The protein produced according to such methods is also provided by the present invention. Preferred embodiments include those in which the protein produced by such process is a mature form of the protein.

Protein compositions of the present invention may further comprise a pharmaceutically acceptable carrier. Compositions comprising an antibody which specifically reacts with such protein are also provided by the present invention.

Methods are also provided for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition comprising a protein of the present invention and a pharmaceutically acceptable carrier.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B are schematic representations of the pED6 and pNOTs vectors, respectively, used for deposit of clones disclosed herein.

DETAILED DESCRIPTION

ISOLATED PROTEINS AND POLYNUCLEOTIDES

Nucleotide and amino acid sequences, as presently determined, are reported below for each clone and protein disclosed in the present application. The nucleotide sequence of each clone can readily be determined by sequencing of the deposited clone in accordance with known methods. The predicted amino acid sequence (both full-length and mature) can then be determined from such nucleotide sequence. The amino acid sequence of the protein encoded by a particular clone can also be determined by expression of the clone in a suitable host cell, collecting the protein and determining its sequence. For each disclosed protein applicants have identified what they have determined to be the reading frame best identifiable with sequence information available at the time of filing.

As used herein a "secreted" protein is one which, when expressed in a suitable host cell, is transported across or through a membrane, including transport as a result of signal sequences in its amino acid sequence. "Secreted" proteins include without limitation

proteins secreted wholly (e.g., soluble proteins) or partially (e.g. , receptors) from the cell in which they are expressed. "Secreted" proteins also include without limitation proteins which are transported across the membrane of the endoplasmic reticulum.

Clone "AA35_2"

A polynucleotide of the present invention has been identified as clone "AA35_2". AA35_2 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AA35_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AA35_2 protein").

The nucleotide sequence of AA35_2 as presently determined is reported in SEQ ID NO:1. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AA35_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:2.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AA35_2 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for AA35_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AA35_2 demonstrated at least some similarity with sequences identified as C16789 (Human placenta cDNA 5'-end GEN-529D11), H23653 (yn72e01.r1 Homo sapiens cDNA clone 173976 5' similar to contains Alu repetitive element), L31848 (Homo sapiens serine/threonine kinase receptor 2 (SKR2) gene, 3 alternative splices, 3' ends), U40455 (Human chromosome X cosmid, clones 196B12, 9H11 and 43H9, repeat units and sequence tagged sites), and Z82197 (Human DNA sequence from clone J293L6). The predicted amino acid sequence disclosed herein for AA35_2 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted AA35_2 protein demonstrated at least some similarity to sequences identified as U58658 (unknown [Homo sapiens]) and X55777 (put. ORF [Homo sapiens]). Based upon sequence similarity, AA35_2 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of AA35_2 indicates that it may contain an Alu repetitive element.

Clone "AM42_3"

A polynucleotide of the present invention has been identified as clone "AM42_3". AM42_3 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. AM42_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "AM42_3 protein").

The nucleotide sequence of AM42_3 as presently determined is reported in SEQ ID NO:3. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the AM42_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:4. Amino acids 2 to 14 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 15, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone AM42_3 should be approximately 1400 bp.

The nucleotide sequence disclosed herein for AM42_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. AM42_3 demonstrated at least some similarity with sequences identified as AA109637 (mm01f02.r1 Stratagene mouse kidney (#937315) Mus musculus cDNA clone 520251 5'), AA131170 (zo08e05.s1 Stratagene neuroepithelium NT2RAMI 937234 Homo sapiens cDNA clone 567104 3'), AA131483 (zo08e05.r1 Stratagene neuroepithelium NT2RAMI 937234 Homo sapiens cDNA clone 567104 5'), and AA445683 (vf62h07.r1 Barstead MPLRB1 Mus musculus cDNA clone 848413 5'). Based upon sequence similarity, AM42_3 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the AM42_3 protein sequence centered around amino acid 152 of SEQ ID NO:4.

Clone "BG137_7"

A polynucleotide of the present invention has been identified as clone "BG137_7". BG137_7 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer

analysis of the amino acid sequence of the encoded protein. BG137_7 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "BG137_7 protein").

The nucleotide sequence of BG137_7 as presently determined is reported in SEQ ID NO:5. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the BG137_7 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:6.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone BG137_7 should be approximately 500 bp.

The nucleotide sequence disclosed herein for BG137_7 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. BG137_7 demonstrated at least some similarity with sequences identified as D87683 (Human mRNA for KIAA0243 gene, partial cds). Based upon sequence similarity, BG137_7 proteins and each similar protein or peptide may share at least some activity.

Clone "CH699_1"

A polynucleotide of the present invention has been identified as clone "CH699_1". CH699_1 was isolated from a human fetal kidney cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CH699_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CH699_1 protein").

The nucleotide sequence of CH699_1 as presently determined is reported in SEQ ID NO:7. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CH699_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:8. Amino acids 217 to 229 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 230, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CH699_1 should be approximately 2000 bp.

The nucleotide sequence disclosed herein for CH699_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and

FASTA search protocols. CH699_1 demonstrated at least some similarity with sequences identified as AA155014 (mr99h05.r1 Stratagene mouse embryonic carcinoma (#937317) Mus musculus cDNA clone 605625 5'), AA423476 (ve76d07.r1 Soares mouse mammary gland NbMMG Mus musculus cDNA clone 832141 5'), U79271 (Human clones 23920 and 23921 mRNA sequence), and W72147 (zd70f08.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 346023 3'). The predicted amino acid sequence disclosed herein for CH699_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CH699_1 protein demonstrated at least some similarity to sequences identified as X51591 (beta-myosin heavy chain [Homo sapiens]). Based upon sequence similarity, CH699_1 proteins and each similar protein or peptide may share at least some activity.

Clone "CO851_1"

A polynucleotide of the present invention has been identified as clone "CO851_1". CO851_1 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CO851_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CO851_1 protein").

The nucleotide sequence of the 5' portion of CO851_1 as presently determined is reported in SEQ ID NO:9. An additional internal nucleotide sequence from CO851_1 as presently determined is reported in SEQ ID NO:10. What applicants believe is the proper reading frame and the predicted amino acid sequence encoded by such internal sequence is reported in SEQ ID NO:11. Amino acids 3 to 15 of SEQ ID NO:11 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 16, or are a transmembrane domain. Additional nucleotide sequence from the 3' portion of CO851_1, including the polyA tail, is reported in SEQ ID NO:12.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CO851_1 should be approximately 1800 bp.

The nucleotide sequence disclosed herein for CO851_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CO851_1 demonstrated at least some similarity with sequences identified as AA132585 (zo20c04.r1 Stratagene colon (#937204) Homo sapiens cDNA clone

587430 5'), H51262 (yp83b07.s1 Homo sapiens cDNA clone 194005 3'), W44070 (mc73a09.r1 Soares mouse embryo NbME13.5 14.5 Mus musculus cDNA clone 354136 5'), and X92871 (X.laevis mRNA for an unknown transmembrane protein). The predicted amino acid sequence disclosed herein for CO851_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CO851_1 protein demonstrated at least some similarity to sequences identified as X92871 (unknown transmembrane protein [Xenopus laevis]). Based upon sequence similarity, CO851_1 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of CO851_1 indicates that it may contain an Alu repetitive element.

Clone "CP111_1"

A polynucleotide of the present invention has been identified as clone "CP111_1". CP111_1 was isolated from a human adult salivary gland cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CP111_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CP111_1 protein").

The nucleotide sequence of CP111_1 as presently determined is reported in SEQ ID NO:13. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CP111_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:14. Amino acids 40 to 52 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 53, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CP111_1 should be approximately 3200 bp.

The nucleotide sequence disclosed herein for CP111_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CP111_1 demonstrated at least some similarity with sequences identified as T53688 (ya98g07.r1 Homo sapiens cDNA clone 69756 5') and W70295 (zd58f03.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 344861 3'). The predicted amino acid sequence disclosed herein for CP111_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol.

The predicted CP111_1 protein demonstrated at least some similarity to sequences identified as X88852 (env protein [Primate T-cell lymphotropic]). Based upon sequence similarity, CP111_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts a potential transmembrane domain within the CP111_1 protein sequence centered around amino acid 50 of SEQ ID NO:14.

Clone "CS278_1"

A polynucleotide of the present invention has been identified as clone "CS278_1". CS278_1 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. CS278_1 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "CS278_1 protein").

The nucleotide sequence of CS278_1 as presently determined is reported in SEQ ID NO:15. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the CS278_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:16. Amino acids 52 to 64 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 65, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone CS278_1 should be approximately 4400 bp.

The nucleotide sequence disclosed herein for CS278_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. CS278_1 demonstrated at least some similarity with sequences identified as AA234319 (zr66c07.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 668364 5'), H44192 (yo73f09.r1 Homo sapiens cDNA clone 183593 5'), W18258 (mb86a11.r1 Soares mouse p3NMF19), X76589 (H.sapiens DNA 3' flanking simple sequence region clone wg2c3), and Z74652 (M.musculus mRNA; expressed sequence tag (tcc2)). The predicted amino acid sequence disclosed herein for CS278_1 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted CS278_1 protein demonstrated at least some similarity to sequences identified as M34651 (ORF-3 protein [Suid herpesvirus 1]). The predicted CS278_1 protein also demonstrated at least some similarity to a protein motif, cytochrome P450 cysteine heme-

iron ligand signature. Based upon sequence similarity, CS278_1 proteins and each similar protein or peptide may share at least some activity. The TopPredII computer program predicts five potential transmembrane domains within the CS278_1 protein sequence, which are centered around amino acids 75, 160, 525, 610, and 700 of SEQ ID NO:16, respectively. The nucleotide sequence of CS278_1 may contain GAA simple repeat elements.

Clone "DF968_3"

A polynucleotide of the present invention has been identified as clone "DF968_3". DF968_3 was isolated from a human adult brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DF968_3 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "DF968_3 protein").

The nucleotide sequence of DF968_3 as presently determined is reported in SEQ ID NO:17. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DF968_3 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:18. Amino acids 11 to 23 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 24, or are a transmembrane domain. Another possible DF968_3 reading frame and predicted amino acid sequence is encoded by basepairs 191 to 430 of SEQ ID NO:17 and is reported in SEQ ID NO:33.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DF968_3 should be approximately 1010 bp.

The nucleotide sequence disclosed herein for DF968_3 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DF968_3 demonstrated at least some similarity with sequences identified as AA426010 (zw49e12.s1 Soares total fetus Nb2HF8 9w Homo sapiens cDNA clone 773422 3' similar to contains element LTR5 repetitive element), H18256 (yn48a04.r1 Homo sapiens cDNA clone 171630 5'), and T06820 (EST04709 Homo sapiens cDNA clone HFBDZ29). The predicted amino acid sequence disclosed herein for DF968_3 was searched against the GenPept and GeneSeq amino acid sequence databases using the BLASTX search protocol. The predicted DF968_3 protein demonstrated at least some

similarity to sequences identified as Z38125 (orf, len 112, CAI 0.07). Based upon sequence similarity, DF968_3 proteins and each similar protein or peptide may share at least some activity. The nucleotide sequence of DF968_3 indicates that it may contain repeat sequences.

Clone "DN1120_2"

A polynucleotide of the present invention has been identified as clone "DN1120_2". DN1120_2 was isolated from a human fetal brain cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DN1120_2 is a full-length clone, including the entire coding sequence of a secreted protein (also referred to herein as "DN1120_2 protein").

The nucleotide sequence of DN1120_2 as presently determined is reported in SEQ ID NO:19. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DN1120_2 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:20.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DN1120_2 should be approximately 1000 bp.

The nucleotide sequence disclosed herein for DN1120_2 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DN1120_2 demonstrated at least some similarity with sequences identified as M62256 (EST00323 Homo sapiens cDNA clone HHCH15 similar to Alu repetitive element), M78991 (EST01139 Homo sapiens cDNA clone HHCPG39), Q59179 (Human brain Expressed Sequence Tag EST00323), and Q61084 (Human brain Expressed Sequence Tag EST01139). Based upon sequence similarity, DN1120_2 proteins and each similar protein or peptide may share at least some activity.

Clone "DO589_1"

A polynucleotide of the present invention has been identified as clone "DO589_1". DO589_1 was isolated from a human adult testes cDNA library using methods which are selective for cDNAs encoding secreted proteins (see U.S. Pat. No. 5,536,637), or was identified as encoding a secreted or transmembrane protein on the basis of computer analysis of the amino acid sequence of the encoded protein. DO589_1 is a full-length

clone, including the entire coding sequence of a secreted protein (also referred to herein as "DO589_1 protein").

The nucleotide sequence of DO589_1 as presently determined is reported in SEQ ID NO:21. What applicants presently believe to be the proper reading frame and the predicted amino acid sequence of the DO589_1 protein corresponding to the foregoing nucleotide sequence is reported in SEQ ID NO:22. Amino acids 17 to 29 are a predicted leader/signal sequence, with the predicted mature amino acid sequence beginning at amino acid 30, or are a transmembrane domain.

The EcoRI/NotI restriction fragment obtainable from the deposit containing clone DO589_1 should be approximately 1800 bp.

The nucleotide sequence disclosed herein for DO589_1 was searched against the GenBank and GeneSeq nucleotide sequence databases using BLASTN/BLASTX and FASTA search protocols. DO589_1 demonstrated at least some similarity with sequences identified as AA402420 (zu47e04.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone 741150 3'), AA426621 (zw03a09.r1 Soares NhHMPu S1 Homo sapiens cDNA clone 768184 5'), AA436749 (zv67c10.r1 Soares total fetus Nb2HF8 9w Homo sapiens cDNA clone 758706 5'), H12845 (yj14h06.r1 Homo sapiens cDNA clone 148763 5'), R42350 (yg01b05.s1 Homo sapiens cDNA clone 30909 3'), W02775 (zc65g07.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 327228 3'), W24833 (zc65g07.r1 Soares fetal heart), W58173 (zd19f02.s1 Soares fetal heart NbHH19W Homo sapiens cDNA clone 341115 3' similar to contains Alu repetitive element;contains element L1 repetitive element), and Z82201 (Human DNA sequence from clone J345P10). Based upon sequence similarity, DO589_1 proteins and each similar protein or peptide may share at least some activity.

Deposit of Clones

Clones AA35_2, AM42_3, BG137_7, CH699_1, CO851_1, CP111_1, CS278_1, DF968_3, DN1120_2, and DO589_1 were deposited on January 23, 1997 with the American Type Culture Collection as an original deposit under the Budapest Treaty and were given the accession number ATCC 98303, from which each clone comprising a particular polynucleotide is obtainable. All restrictions on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent, except for the requirements specified in 37 C.F.R. § 1.808(b).

Each clone has been transfected into separate bacterial cells (*E. coli*) in this composite deposit. Each clone can be removed from the vector in which it was deposited

by performing an EcoRI/NotI digestion (5' site, EcoRI; 3' site, NotI) to produce the appropriate fragment for such clone. Each clone was deposited in either the pED6 or pNOTs vector depicted in Fig. 1. The pED6dpc2 vector ("pED6") was derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning (Kaufman *et al.*, 1991, *Nucleic Acids Res.* **19**: 4485-4490); the pNOTs vector was derived from pMT2 (Kaufman *et al.*, 1989, *Mol. Cell. Biol.* **9**: 946-958) by deletion of the DHFR sequences, insertion of a new polylinker, and insertion of the M13 origin of replication in the ClaI site. In some instances, the deposited clone can become "flipped" (i.e., in the reverse orientation) in the deposited isolate. In such instances, the cDNA insert can still be isolated by digestion with EcoRI and NotI. However, NotI will then produce the 5' site and EcoRI will produce the 3' site for placement of the cDNA in proper orientation for expression in a suitable vector. The cDNA may also be expressed from the vectors in which they were deposited.

Bacterial cells containing a particular clone can be obtained from the composite deposit as follows:

An oligonucleotide probe or probes should be designed to the sequence that is known for that particular clone. This sequence can be derived from the sequences provided herein, or from a combination of those sequences. The sequence of the oligonucleotide probe that was used to isolate each full-length clone is identified below, and should be most reliable in isolating the clone of interest.

Clone	Probe Sequence
AA35_2	SEQ ID NO:23
AM42_3	SEQ ID NO:24
BG137_7	SEQ ID NO:25
CH699_1	SEQ ID NO:26
CO851_1	SEQ ID NO:27
CP111_1	SEQ ID NO:28
CS278_1	SEQ ID NO:29
DF968_3	SEQ ID NO:30
DN1120_2	SEQ ID NO:31
DO589_1	SEQ ID NO:32

In the sequences listed above which include an N at position 2, that position is occupied in preferred probes/primers by a biotinylated phosphoaramidite residue rather than a nucleotide (such as , for example, that produced by use of biotin phosphoramidite (1-dimethoxytrityloxy-2-(N-biotinyl-4-aminobutyl)-propyl-3-O-(2-cyanoethyl)-(N,N-diisopropyl)-phosphoramadite) (Glen Research, cat. no. 10-1953)).

The design of the oligonucleotide probe should preferably follow these parameters:

(a) It should be designed to an area of the sequence which has the fewest ambiguous bases ("N's"), if any;

(b) It should be designed to have a T_m of approx. 80 ° C (assuming 2° for each A or T and 4 degrees for each G or C).

The oligonucleotide should preferably be labeled with g-^{32}P ATP (specific activity 6000 Ci/mmole) and T4 polynucleotide kinase using commonly employed techniques for labeling oligonucleotides. Other labeling techniques can also be used. Unincorporated label should preferably be removed by gel filtration chromatography or other established methods. The amount of radioactivity incorporated into the probe should be quantitated by measurement in a scintillation counter. Preferably, specific activity of the resulting probe should be approximately 4e+6 dpm/pmole.

The bacterial culture containing the pool of full-length clones should preferably be thawed and 100 µl of the stock used to inoculate a sterile culture flask containing 25 ml of sterile L-broth containing ampicillin at 100 µg/ml. The culture should preferably be grown to saturation at 37°C, and the saturated culture should preferably be diluted in fresh L-broth. Aliquots of these dilutions should preferably be plated to determine the dilution and volume which will yield approximately 5000 distinct and well-separated colonies on solid bacteriological media containing L-broth containing ampicillin at 100 µg/ml and agar at 1.5% in a 150 mm petri dish when grown overnight at 37°C. Other known methods of obtaining distinct, well-separated colonies can also be employed.

Standard colony hybridization procedures should then be used to transfer the colonies to nitrocellulose filters and lyse, denature and bake them.

The filter is then preferably incubated at 65°C for 1 hour with gentle agitation in 6X SSC (20X stock is 175.3 g NaCl/liter, 88.2 g Na citrate/liter, adjusted to pH 7.0 with NaOH) containing 0.5% SDS, 100 µg/ml of yeast RNA, and 10 mM EDTA (approximately 10 mL per 150 mm filter). Preferably, the probe is then added to the hybridization mix at a concentration greater than or equal to 1e+6 dpm/mL. The filter is then preferably

incubated at 65°C with gentle agitation overnight. The filter is then preferably washed in 500 mL of 2X SSC/0.5% SDS at room temperature without agitation, preferably followed by 500 mL of 2X SSC/0.1% SDS at room temperature with gentle shaking for 15 minutes. A third wash with 0.1X SSC/0.5% SDS at 65°C for 30 minutes to 1 hour is optional. The filter is then preferably dried and subjected to autoradiography for sufficient time to visualize the positives on the X-ray film. Other known hybridization methods can also be employed.

The positive colonies are picked, grown in culture, and plasmid DNA isolated using standard procedures. The clones can then be verified by restriction analysis, hybridization analysis, or DNA sequencing.

Fragments of the proteins of the present invention which are capable of exhibiting biological activity are also encompassed by the present invention. Fragments of the protein may be in linear form or they may be cyclized using known methods, for example, as described in H.U. Saragovi, *et al.*, Bio/Technology 10, 773-778 (1992) and in R.S. McDowell, *et al.*, J. Amer. Chem. Soc. 114, 9245-9253 (1992), both of which are incorporated herein by reference. Such fragments may be fused to carrier molecules such as immunoglobulins for many purposes, including increasing the valency of protein binding sites. For example, fragments of the protein may be fused through "linker" sequences to the Fc portion of an immunoglobulin. For a bivalent form of the protein, such a fusion could be to the Fc portion of an IgG molecule. Other immunoglobulin isotypes may also be used to generate such fusions. For example, a protein - IgM fusion would generate a decavalent form of the protein of the invention.

The present invention also provides both full-length and mature forms of the disclosed proteins. The full-length form of the such proteins is identified in the sequence listing by translation of the nucleotide sequence of each disclosed clone. The mature form of such protein may be obtained by expression of the disclosed full-length polynucleotide (preferably those deposited with ATCC) in a suitable mammalian cell or other host cell. The sequence of the mature form of the protein may also be determinable from the amino acid sequence of the full-length form.

The present invention also provides genes corresponding to the polynucleotide sequences disclosed herein. "Corresponding genes" are the regions of the genome that are transcribed to produce the mRNAs from which cDNA polynucleotide sequences are derived and may include contiguous regions of the genome necessary for the regulated expression of such genes. Corresponding genes may therefore include but are not limited

to coding sequences, 5' and 3' untranslated regions, alternatively spliced exons, introns, promoters, enhancers, and silencer or suppressor elements. The corresponding genes can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include the preparation of probes or primers from the disclosed sequence information for identification and/or amplification of genes in appropriate genomic libraries or other sources of genomic materials. An "isolated gene" is a gene that has been separated from the adjacent coding sequences, if any, present in the genome of the organism from which the gene was isolated.

Organisms that have enhanced, reduced, or modified expression of the gene(s) corresponding to the polynucleotide sequences disclosed herein are provided. The desired change in gene expression can be achieved through the use of antisense polynucleotides or ribozymes that bind and/or cleave the mRNA transcribed from the gene (Albert and Morris, 1994, *Trends Pharmacol. Sci.* **15(7)**: 250-254; Lavarosky *et al.*, 1997, *Biochem. Mol. Med.* **62(1)**: 11-22; and Hampel, 1998, *Prog. Nucleic Acid Res. Mol. Biol.* **58**: 1-39; all of which are incorporated by reference herein). Transgenic animals that have multiple copies of the gene(s) corresponding to the polynucleotide sequences disclosed herein, preferably produced by transformation of cells with genetic constructs that are stably maintained within the transformed cells and their progeny, are provided. Transgenic animals that have modified genetic control regions that increase or reduce gene expression levels, or that change temporal or spatial patterns of gene expression, are also provided (see European Patent No. 0 649 464 B1, incorporated by reference herein). In addition, organisms are provided in which the gene(s) corresponding to the polynucleotide sequences disclosed herein have been partially or completely inactivated, through insertion of extraneous sequences into the corresponding gene(s) or through deletion of all or part of the corresponding gene(s). Partial or complete gene inactivation can be accomplished through insertion, preferably followed by imprecise excision, of transposable elements (Plasterk, 1992, *Bioessays* **14(9)**: 629-633; Zwaal *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* **90(16)**: 7431-7435; Clark *et al.*, 1994, *Proc. Natl. Acad. Sci. USA* **91(2)**: 719-722; all of which are incorporated by reference herein), or through homologous recombination, preferably detected by positive/negative genetic selection strategies (Mansour *et al.*, 1988, *Nature* **336**: 348-352; U.S. Patent Nos. 5,464,764; 5,487,992; 5,627,059; 5,631,153; 5,614, 396; 5,616,491; and 5,679,523; all of which are incorporated by reference herein). These organisms with altered gene expression are preferably eukaryotes and more preferably are mammals. Such organisms are useful for the development of non-human models for

the study of disorders involving the corresponding gene(s), and for the development of assay systems for the identification of molecules that interact with the protein product(s) of the corresponding gene(s).

Where the protein of the present invention is membrane-bound (e.g., is a receptor), the present invention also provides for soluble forms of such protein. In such forms part or all of the intracellular and transmembrane domains of the protein are deleted such that the protein is fully secreted from the cell in which it is expressed. The intracellular and transmembrane domains of proteins of the invention can be identified in accordance with known techniques for determination of such domains from sequence information.

Proteins and protein fragments of the present invention include proteins with amino acid sequence lengths that are at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of a disclosed protein and have at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with that disclosed protein, where sequence identity is determined by comparing the amino acid sequences of the proteins when aligned so as to maximize overlap and identity while minimizing sequence gaps. Also included in the present invention are proteins and protein fragments that contain a segment preferably comprising 8 or more (more preferably 20 or more, most preferably 30 or more) contiguous amino acids that shares at least 75% sequence identity (more preferably, at least 85% identity; most preferably at least 95% identity) with any such segment of any of the disclosed proteins.

Species homologs of the disclosed polynucleotides and proteins are also provided by the present invention. As used herein, a "species homologue" is a protein or polynucleotide with a different species of origin from that of a given protein or polynucleotide, but with significant sequence similarity to the given protein or polynucleotide, as determined by those of skill in the art. Species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source from the desired species.

The invention also encompasses allelic variants of the disclosed polynucleotides or proteins; that is, naturally-occurring alternative forms of the isolated polynucleotide which also encode proteins which are identical, homologous, or related to that encoded by the polynucleotides .

The invention also includes polynucleotides with sequences complementary to those of the polynucleotides disclosed herein.

The present invention also includes polynucleotides capable of hybridizing under reduced stringency conditions, more preferably stringent conditions, and most preferably highly stringent conditions, to polynucleotides described herein. Examples of stringency conditions are shown in the table below: highly stringent conditions are those that are at least as stringent as, for example, conditions A-F; stringent conditions are at least as stringent as, for example, conditions G-L; and reduced stringency conditions are at least as stringent as, for example, conditions M-R.

Stringency Condition	Polynucleotide Hybrid	Hybrid Length (bp)‡	Hybridization Temperature and Buffer†	Wash Temperature and Buffer†
A	DNA:DNA	≥ 50	65°C; 1xSSC -or- 42°C; 1xSSC, 50% formamide	65°C; 0.3xSSC
B	DNA:DNA	<50	T_B*; 1xSSC	T_B*; 1xSSC
C	DNA:RNA	≥ 50	67°C; 1xSSC -or- 45°C; 1xSSC, 50% formamide	67°C; 0.3xSSC
D	DNA:RNA	<50	T_D*; 1xSSC	T_D*; 1xSSC
E	RNA:RNA	≥ 50	70°C; 1xSSC -or- 50°C; 1xSSC, 50% formamide	70°C; 0.3xSSC
F	RNA:RNA	<50	T_F*; 1xSSC	T_F*; 1xSSC
G	DNA:DNA	≥ 50	65°C; 4xSSC -or- 42°C; 4xSSC, 50% formamide	65°C; 1xSSC
H	DNA:DNA	<50	T_H*; 4xSSC	T_H*; 4xSSC
I	DNA:RNA	≥ 50	67°C; 4xSSC -or- 45°C; 4xSSC, 50% formamide	67°C; 1xSSC
J	DNA:RNA	<50	T_J*; 4xSSC	T_J*; 4xSSC
K	RNA:RNA	≥ 50	70°C; 4xSSC -or- 50°C; 4xSSC, 50% formamide	67°C; 1xSSC
L	RNA:RNA	<50	T_L*; 2xSSC	T_L*; 2xSSC
M	DNA:DNA	≥ 50	50°C; 4xSSC -or- 40°C; 6xSSC, 50% formamide	50°C; 2xSSC
N	DNA:DNA	<50	T_N*; 6xSSC	T_N*; 6xSSC
O	DNA:RNA	≥ 50	55°C; 4xSSC -or- 42°C; 6xSSC, 50% formamide	55°C; 2xSSC
P	DNA:RNA	<50	T_P*; 6xSSC	T_P*; 6xSSC
Q	RNA:RNA	≥ 50	60°C; 4xSSC -or- 45°C; 6xSSC, 50% formamide	60°C; 2xSSC
R	RNA:RNA	<50	T_R*; 4xSSC	T_R*; 4xSSC

‡: The hybrid length is that anticipated for the hybridized region(s) of the hybridizing polynucleotides. When hybridizing a polynucleotide to a target polynucleotide of unknown sequence, the hybrid length is assumed

to be that of the hybridizing polynucleotide. When polynucleotides of known sequence are hybridized, the hybrid length can be determined by aligning the sequences of the polynucleotides and identifying the region or regions of optimal sequence complementarity.

[†]: SSPE (1xSSPE is 0.15M NaCl, 10mM NaH_2PO_4, and 1.25mM EDTA, pH 7.4) can be substituted for SSC (1xSSC is 0.15M NaCl and 15mM sodium citrate) in the hybridization and wash buffers; washes are performed for 15 minutes after hybridization is complete.

[*]$T_B - T_R$: The hybridization temperature for hybrids anticipated to be less than 50 base pairs in length should be 5-10°C less than the melting temperature (T_m) of the hybrid, where T_m is determined according to the following equations. For hybrids less than 18 base pairs in length, $T_m(°C) = 2(\#\text{ of A + T bases}) + 4(\#\text{ of G + C bases})$. For hybrids between 18 and 49 base pairs in length, $T_m(°C) = 81.5 + 16.6(\log_{10}[Na^+]) + 0.41(\%G+C) - (600/N)$, where N is the number of bases in the hybrid, and $[Na^+]$ is the concentration of sodium ions in the hybridization buffer ($[Na^+]$ for 1xSSC = 0.165 M).

Additional examples of stringency conditions for polynucleotide hybridization are provided in Sambrook, J., E.F. Fritsch, and T. Maniatis, 1989, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, chapters 9 and 11, and *Current Protocols in Molecular Biology*, 1995, F.M. Ausubel et al., eds., John Wiley & Sons, Inc., sections 2.10 and 6.3-6.4, incorporated herein by reference.

Preferably, each such hybridizing polynucleotide has a length that is at least 25%(more preferably at least 50%, and most preferably at least 75%) of the length of the polynucleotide of the present invention to which it hybridizes, and has at least 60% sequence identity (more preferably, at least 75% identity; most preferably at least 90% or 95% identity) with the polynucleotide of the present invention to which it hybridizes, where sequence identity is determined by comparing the sequences of the hybridizing polynucleotides when aligned so as to maximize overlap and identity while minimizing sequence gaps.

The isolated polynucleotide of the invention may be operably linked to an expression control sequence such as the pMT2 or pED expression vectors disclosed in Kaufman *et al.*, Nucleic Acids Res. 19, 4485-4490 (1991), in order to produce the protein recombinantly. Many suitable expression control sequences are known in the art. General methods of expressing recombinant proteins are also known and are exemplified in R. Kaufman, Methods in Enzymology 185, 537-566 (1990). As defined herein "operably linked" means that the isolated polynucleotide of the invention and an expression control sequence are situated within a vector or cell in such a way that the protein is expressed by a host cell which has been transformed (transfected) with the ligated polynucleotide/expression control sequence.

A number of types of cells may act as suitable host cells for expression of the protein. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205

cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from in vitro culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

Alternatively, it may be possible to produce the protein in lower eukaryotes such as yeast or in prokaryotes such as bacteria. Potentially suitable yeast strains include *Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces* strains, *Candida*, or any yeast strain capable of expressing heterologous proteins. Potentially suitable bacterial strains include *Escherichia coli, Bacillus subtilis, Salmonella typhimurium*, or any bacterial strain capable of expressing heterologous proteins. If the protein is made in yeast or bacteria, it may be necessary to modify the protein produced therein, for example by phosphorylation or glycosylation of the appropriate sites, in order to obtain the functional protein. Such covalent attachments may be accomplished using known chemical or enzymatic methods.

The protein may also be produced by operably linking the isolated polynucleotide of the invention to suitable control sequences in one or more insect expression vectors, and employing an insect expression system. Materials and methods for baculovirus/insect cell expression systems are commercially available in kit form from, *e.g.*, Invitrogen, San Diego, California, U.S.A. (the MaxBac® kit), and such methods are well known in the art, as described in Summers and Smith, Texas Agricultural Experiment Station Bulletin No. 1555 (1987), incorporated herein by reference. As used herein, an insect cell capable of expressing a polynucleotide of the present invention is "transformed."

The protein of the invention may be prepared by culturing transformed host cells under culture conditions suitable to express the recombinant protein. The resulting expressed protein may then be purified from such culture (i.e., from culture medium or cell extracts) using known purification processes, such as gel filtration and ion exchange chromatography. The purification of the protein may also include an affinity column containing agents which will bind to the protein; one or more column steps over such affinity resins as concanavalin A-agarose, heparin-toyopearl® or Cibacrom blue 3GA Sepharose®; one or more steps involving hydrophobic interaction chromatography using such resins as phenyl ether, butyl ether, or propyl ether; or immunoaffinity chromatography.

Alternatively, the protein of the invention may also be expressed in a form which will facilitate purification. For example, it may be expressed as a fusion protein, such as

those of maltose binding protein (MBP), glutathione-S-transferase (GST) or thioredoxin (TRX). Kits for expression and purification of such fusion proteins are commercially available from New England BioLab (Beverly, MA), Pharmacia (Piscataway, NJ) and InVitrogen, respectively. The protein can also be tagged with an epitope and subsequently purified by using a specific antibody directed to such epitope. One such epitope ("Flag") is commercially available from Kodak (New Haven, CT).

Finally, one or more reverse-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify the protein. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a substantially homogeneous isolated recombinant protein. The protein thus purified is substantially free of other mammalian proteins and is defined in accordance with the present invention as an "isolated protein."

The protein of the invention may also be expressed as a product of transgenic animals, e.g., as a component of the milk of transgenic cows, goats, pigs, or sheep which are characterized by somatic or germ cells containing a nucleotide sequence encoding the protein.

The protein may also be produced by known conventional chemical synthesis. Methods for constructing the proteins of the present invention by synthetic means are known to those skilled in the art. The synthetically-constructed protein sequences, by virtue of sharing primary, secondary or tertiary structural and/or conformational characteristics with proteins may possess biological properties in common therewith, including protein activity. Thus, they may be employed as biologically active or immunological substitutes for natural, purified proteins in screening of therapeutic compounds and in immunological processes for the development of antibodies.

The proteins provided herein also include proteins characterized by amino acid sequences similar to those of purified proteins but into which modification are naturally provided or deliberately engineered. For example, modifications in the peptide or DNA sequences can be made by those skilled in the art using known techniques. Modifications of interest in the protein sequences may include the alteration, substitution, replacement, insertion or deletion of a selected amino acid residue in the coding sequence. For example, one or more of the cysteine residues may be deleted or replaced with another amino acid to alter the conformation of the molecule. Techniques for such alteration, substitution, replacement, insertion or deletion are well known to those skilled in the art

(see, e.g., U.S. Patent No. 4,518,584). Preferably, such alteration, substitution, replacement, insertion or deletion retains the desired activity of the protein.

Other fragments and derivatives of the sequences of proteins which would be expected to retain protein activity in whole or in part and may thus be useful for screening or other immunological methodologies may also be easily made by those skilled in the art given the disclosures herein. Such modifications are believed to be encompassed by the present invention.

USES AND BIOLOGICAL ACTIVITY

The polynucleotides and proteins of the present invention are expected to exhibit one or more of the uses or biological activities (including those associated with assays cited herein) identified below. Uses or activities described for proteins of the present invention may be provided by administration or use of such proteins or by administration or use of polynucleotides encoding such proteins (such as, for example, in gene therapies or vectors suitable for introduction of DNA).

Research Uses and Utilities

The polynucleotides provided by the present invention can be used by the research community for various purposes. The polynucleotides can be used to express recombinant protein for analysis, characterization or therapeutic use; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in disease states); as molecular weight markers on Southern gels; as chromosome markers or tags (when labeled) to identify chromosomes or to map related gene positions; to compare with endogenous DNA sequences in patients to identify potential genetic disorders; as probes to hybridize and thus discover novel, related DNA sequences; as a source of information to derive PCR primers for genetic fingerprinting; as a probe to "subtract-out" known sequences in the process of discovering other novel polynucleotides; for selecting and making oligomers for attachment to a "gene chip" or other support, including for examination of expression patterns; to raise anti-protein antibodies using DNA immunization techniques; and as an antigen to raise anti-DNA antibodies or elicit another immune response. Where the polynucleotide encodes a protein which binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the polynucleotide can also be used in interaction trap assays (such as, for example, that

described in Gyuris et al., Cell 75:791-803 (1993)) to identify polynucleotides encoding the other protein with which binding occurs or to identify inhibitors of the binding interaction.

The proteins provided by the present invention can similarly be used in assay to determine biological activity, including in a panel of multiple proteins for high-throughput screening; to raise antibodies or to elicit another immune response; as a reagent (including the labeled reagent) in assays designed to quantitatively determine levels of the protein (or its receptor) in biological fluids; as markers for tissues in which the corresponding protein is preferentially expressed (either constitutively or at a particular stage of tissue differentiation or development or in a disease state); and, of course, to isolate correlative receptors or ligands. Where the protein binds or potentially binds to another protein (such as, for example, in a receptor-ligand interaction), the protein can be used to identify the other protein with which binding occurs or to identify inhibitors of the binding interaction. Proteins involved in these binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction.

Any or all of these research utilities are capable of being developed into reagent grade or kit format for commercialization as research products.

Methods for performing the uses listed above are well known to those skilled in the art. References disclosing such methods include without limitation "Molecular Cloning: A Laboratory Manual", 2d ed., Cold Spring Harbor Laboratory Press, Sambrook, J., E.F. Fritsch and T. Maniatis eds., 1989, and "Methods in Enzymology: Guide to Molecular Cloning Techniques", Academic Press, Berger, S.L. and A.R. Kimmel eds., 1987.

Nutritional Uses

Polynucleotides and proteins of the present invention can also be used as nutritional sources or supplements. Such uses include without limitation use as a protein or amino acid supplement, use as a carbon source, use as a nitrogen source and use as a source of carbohydrate. In such cases the protein or polynucleotide of the invention can be added to the feed of a particular organism or can be administered as a separate solid or liquid preparation, such as in the form of powder, pills, solutions, suspensions or capsules. In the case of microorganisms, the protein or polynucleotide of the invention can be added to the medium in or on which the microorganism is cultured.

Cytokine and Cell Proliferation/Differentiation Activity

A protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a protein of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines including, without limitation, 32D, DA2, DA1G, T10, B9, B9/11, BaF3, MC9/G, M+ (preB M+), 2E8, RB5, DA1, 123, T1165, HT2, CTLL2, TF-1, Mo7e and CMK.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for T-cell or thymocyte proliferation include without limitation those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Bertagnolli et al., J. Immunol. 145:1706-1712, 1990; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Bertagnolli, et al., J. Immunol. 149:3778-3783, 1992; Bowman et al., J. Immunol. 152: 1756-1761, 1994.

Assays for cytokine production and/or proliferation of spleen cells, lymph node cells or thymocytes include, without limitation, those described in: Polyclonal T cell stimulation, Kruisbeek, A.M. and Shevach, E.M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.12.1-3.12.14, John Wiley and Sons, Toronto. 1994; and Measurement of mouse and human Interferon γ, Schreiber, R.D. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.8.1-6.8.8, John Wiley and Sons, Toronto. 1994.

Assays for proliferation and differentiation of hematopoietic and lymphopoietic cells include, without limitation, those described in: Measurement of Human and Murine Interleukin 2 and Interleukin 4, Bottomly, K., Davis, L.S. and Lipsky, P.E. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.3.1-6.3.12, John Wiley and Sons, Toronto. 1991; deVries et al., J. Exp. Med. 173:1205-1211, 1991; Moreau et al., Nature 336:690-692, 1988; Greenberger et al., Proc. Natl. Acad. Sci. U.S.A. 80:2931-2938, 1983; Measurement of mouse and human interleukin 6 - Nordan, R. In *Current Protocols in*

Immunology. J.E.e.a. Coligan eds. Vol 1 pp. 6.6.1-6.6.5, John Wiley and Sons, Toronto. 1991; Smith et al., Proc. Natl. Acad. Sci. U.S.A. 83:1857-1861, 1986; Measurement of human Interleukin 11 - Bennett, F., Giannotti, J., Clark, S.C. and Turner, K. J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.15.1 John Wiley and Sons, Toronto. 1991; Measurement of mouse and human Interleukin 9 - Ciarletta, A., Giannotti, J., Clark, S.C. and Turner, K.J. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 6.13.1, John Wiley and Sons, Toronto. 1991.

Assays for T-cell clone responses to antigens (which will identify, among others, proteins that affect APC-T cell interactions as well as direct T-cell effects by measuring proliferation and cytokine production) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function; Chapter 6, Cytokines and their cellular receptors; Chapter 7, Immunologic studies in Humans); Weinberger et al., Proc. Natl. Acad. Sci. USA 77:6091-6095, 1980; Weinberger et al., Eur. J. Immun. 11:405-411, 1981; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988.

Immune Stimulating or Suppressing Activity

A protein of the present invention may also exhibit immune stimulating or immune suppressing activity, including without limitation the activities for which assays are described herein. A protein may be useful in the treatment of various immune deficiencies and disorders (including severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral (e.g., HIV) as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using a protein of the present invention, including infections by HIV, hepatitis viruses, herpesviruses, mycobacteria, Leishmania spp., malaria spp. and various fungal infections such as candidiasis. Of course, in this regard, a protein of the present invention may also be useful where a boost to the immune system generally may be desirable, *i.e.*, in the treatment of cancer.

Autoimmune disorders which may be treated using a protein of the present invention include, for example, connective tissue disease, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin dependent diabetes mellitis, myasthenia gravis, graft-versus-host disease and autoimmune inflammatory eye disease. Such a protein of the present invention may also to be useful in the treatment of allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems. Other conditions, in which immune suppression is desired (including, for example, organ transplantation), may also be treatable using a protein of the present invention.

Using the proteins of the invention it may also be possible to immune responses, in a number of ways. Down regulation may be in the form of inhibiting or blocking an immune response already in progress or may involve preventing the induction of an immune response. The functions of activated T cells may be inhibited by suppressing T cell responses or by inducing specific tolerance in T cells, or both. Immunosuppression of T cell responses is generally an active, non-antigen-specific, process which requires continuous exposure of the T cells to the suppressive agent. Tolerance, which involves inducing non-responsiveness or anergy in T cells, is distinguishable from immunosuppression in that it is generally antigen-specific and persists after exposure to the tolerizing agent has ceased. Operationally, tolerance can be demonstrated by the lack of a T cell response upon reexposure to specific antigen in the absence of the tolerizing agent.

Down regulating or preventing one or more antigen functions (including without limitation B lymphocyte antigen functions (such as , for example, B7)), *e.g.*, preventing high level lymphokine synthesis by activated T cells, will be useful in situations of tissue, skin and organ transplantation and in graft-versus-host disease (GVHD). For example, blockage of T cell function should result in reduced tissue destruction in tissue transplantation. Typically, in tissue transplants, rejection of the transplant is initiated through its recognition as foreign by T cells, followed by an immune reaction that destroys the transplant. The administration of a molecule which inhibits or blocks interaction of a B7 lymphocyte antigen with its natural ligand(s) on immune cells (such as a soluble, monomeric form of a peptide having B7-2 activity alone or in conjunction with a monomeric form of a peptide having an activity of another B lymphocyte antigen (*e.g.*, B7-1, B7-3) or blocking antibody), prior to transplantation can lead to the binding of the

molecule to the natural ligand(s) on the immune cells without transmitting the corresponding costimulatory signal. Blocking B lymphocyte antigen function in this matter prevents cytokine synthesis by immune cells, such as T cells, and thus acts as an immunosuppressant. Moreover, the lack of costimulation may also be sufficient to anergize the T cells, thereby inducing tolerance in a subject. Induction of long-term tolerance by B lymphocyte antigen-blocking reagents may avoid the necessity of repeated administration of these blocking reagents. To achieve sufficient immunosuppression or tolerance in a subject, it may also be necessary to block the function of a combination of B lymphocyte antigens.

The efficacy of particular blocking reagents in preventing organ transplant rejection or GVHD can be assessed using animal models that are predictive of efficacy in humans. Examples of appropriate systems which can be used include allogeneic cardiac grafts in rats and xenogeneic pancreatic islet cell grafts in mice, both of which have been used to examine the immunosuppressive effects of CTLA4Ig fusion proteins *in vivo* as described in Lenschow *et al.*, Science *257*:789-792 (1992) and Turka *et al.*, Proc. Natl. Acad. Sci USA, *89*:11102-11105 (1992). In addition, murine models of GVHD (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 846-847) can be used to determine the effect of blocking B lymphocyte antigen function *in vivo* on the development of that disease.

Blocking antigen function may also be therapeutically useful for treating autoimmune diseases. Many autoimmune disorders are the result of inappropriate activation of T cells that are reactive against self tissue and which promote the production of cytokines and autoantibodies involved in the pathology of the diseases. Preventing the activation of autoreactive T cells may reduce or eliminate disease symptoms. Administration of reagents which block costimulation of T cells by disrupting receptor:ligand interactions of B lymphocyte antigens can be used to inhibit T cell activation and prevent production of autoantibodies or T cell-derived cytokines which may be involved in the disease process. Additionally, blocking reagents may induce antigen-specific tolerance of autoreactive T cells which could lead to long-term relief from the disease. The efficacy of blocking reagents in preventing or alleviating autoimmune disorders can be determined using a number of well-characterized animal models of human autoimmune diseases. Examples include murine experimental autoimmune encephalitis, systemic lupus erythmatosis in MRL/*lpr/lpr* mice or NZB hybrid mice, murine autoimmune collagen arthritis, diabetes mellitus in NOD mice and BB rats, and

murine experimental myasthenia gravis (see Paul ed., Fundamental Immunology, Raven Press, New York, 1989, pp. 840-856).

Upregulation of an antigen function (preferably a B lymphocyte antigen function), as a means of up regulating immune responses, may also be useful in therapy. Upregulation of immune responses may be in the form of enhancing an existing immune response or eliciting an initial immune response. For example, enhancing an immune response through stimulating B lymphocyte antigen function may be useful in cases of viral infection. In addition, systemic viral diseases such as influenza, the common cold, and encephalitis might be alleviated by the administration of stimulatory forms of B lymphocyte antigens systemically.

Alternatively, anti-viral immune responses may be enhanced in an infected patient by removing T cells from the patient, costimulating the T cells *in vitro* with viral antigen-pulsed APCs either expressing a peptide of the present invention or together with a stimulatory form of a soluble peptide of the present invention and reintroducing the *in vitro* activated T cells into the patient. Another method of enhancing anti-viral immune responses would be to isolate infected cells from a patient, transfect them with a nucleic acid encoding a protein of the present invention as described herein such that the cells express all or a portion of the protein on their surface, and reintroduce the transfected cells into the patient. The infected cells would now be capable of delivering a costimulatory signal to, and thereby activate, T cells *in vivo*.

In another application, up regulation or enhancement of antigen function (preferably B lymphocyte antigen function) may be useful in the induction of tumor immunity. Tumor cells (*e.g.*, sarcoma, melanoma, lymphoma, leukemia, neuroblastoma, carcinoma) transfected with a nucleic acid encoding at least one peptide of the present invention can be administered to a subject to overcome tumor-specific tolerance in the subject. If desired, the tumor cell can be transfected to express a combination of peptides. For example, tumor cells obtained from a patient can be transfected *ex vivo* with an expression vector directing the expression of a peptide having B7-2-like activity alone, or in conjunction with a peptide having B7-1-like activity and/or B7-3-like activity. The transfected tumor cells are returned to the patient to result in expression of the peptides on the surface of the transfected cell. Alternatively, gene therapy techniques can be used to target a tumor cell for transfection *in vivo*.

The presence of the peptide of the present invention having the activity of a B lymphocyte antigen(s) on the surface of the tumor cell provides the necessary

costimulation signal to T cells to induce a T cell mediated immune response against the transfected tumor cells. In addition, tumor cells which lack MHC class I or MHC class II molecules, or which fail to reexpress sufficient amounts of MHC class I or MHC class II molecules, can be transfected with nucleic acid encoding all or a portion of (*e.g.*, a cytoplasmic-domain truncated portion) of an MHC class I α chain protein and β_2 microglobulin protein or an MHC class II α chain protein and an MHC class II β chain protein to thereby express MHC class I or MHC class II proteins on the cell surface. Expression of the appropriate class I or class II MHC in conjunction with a peptide having the activity of a B lymphocyte antigen (*e.g.*, B7-1, B7-2, B7-3) induces a T cell mediated immune response against the transfected tumor cell. Optionally, a gene encoding an antisense construct which blocks expression of an MHC class II associated protein, such as the invariant chain, can also be cotransfected with a DNA encoding a peptide having the activity of a B lymphocyte antigen to promote presentation of tumor associated antigens and induce tumor specific immunity. Thus, the induction of a T cell mediated immune response in a human subject may be sufficient to overcome tumor-specific tolerance in the subject.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for thymocyte or splenocyte cytotoxicity include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Herrmann et al., Proc. Natl. Acad. Sci. USA 78:2488-2492, 1981; Herrmann et al., J. Immunol. 128:1968-1974, 1982; Handa et al., J. Immunol. 135:1564-1572, 1985; Takai et al., J. Immunol. 137:3494-3500, 1986; Bowmanet al., J. Virology 61:1992-1998; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., Cellular Immunology 133:327-341, 1991; Brown et al., J. Immunol. 153:3079-3092, 1994.

Assays for T-cell-dependent immunoglobulin responses and isotype switching (which will identify, among others, proteins that modulate T-cell dependent antibody responses and that affect Th1/Th2 profiles) include, without limitation, those described in: Maliszewski, J. Immunol. 144:3028-3033, 1990; and Assays for B cell function: *In vitro*

antibody production, Mond, J.J. and Brunswick, M. In *Current Protocols in Immunology*. J.E.e.a. Coligan eds. Vol 1 pp. 3.8.1-3.8.16, John Wiley and Sons, Toronto. 1994.

Mixed lymphocyte reaction (MLR) assays (which will identify, among others, proteins that generate predominantly Th1 and CTL responses) include, without limitation, those described in: Current Protocols in Immunology, Ed by J. E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 3, In Vitro assays for Mouse Lymphocyte Function 3.1-3.19; Chapter 7, Immunologic studies in Humans); Takai et al., J. Immunol. 137:3494-3500, 1986; Takai et al., J. Immunol. 140:508-512, 1988; Bertagnolli et al., J. Immunol. 149:3778-3783, 1992.

Dendritic cell-dependent assays (which will identify, among others, proteins expressed by dendritic cells that activate naive T-cells) include, without limitation, those described in: Guery et al., J. Immunol. 134:536-544, 1995; Inaba et al., Journal of Experimental Medicine 173:549-559, 1991; Macatonia et al., Journal of Immunology 154:5071-5079, 1995; Porgador et al., Journal of Experimental Medicine 182:255-260, 1995; Nair et al., Journal of Virology 67:4062-4069, 1993; Huang et al., Science 264:961-965, 1994; Macatonia et al., Journal of Experimental Medicine 169:1255-1264, 1989; Bhardwaj et al., Journal of Clinical Investigation 94:797-807, 1994; and Inaba et al., Journal of Experimental Medicine 172:631-640, 1990.

Assays for lymphocyte survival/apoptosis (which will identify, among others, proteins that prevent apoptosis after superantigen induction and proteins that regulate lymphocyte homeostasis) include, without limitation, those described in: Darzynkiewicz et al., Cytometry 13:795-808, 1992; Gorczyca et al., Leukemia 7:659-670, 1993; Gorczyca et al., Cancer Research 53:1945-1951, 1993; Itoh et al., Cell 66:233-243, 1991; Zacharchuk, Journal of Immunology 145:4037-4045, 1990; Zamai et al., Cytometry 14:891-897, 1993; Gorczyca et al., International Journal of Oncology 1:639-648, 1992.

Assays for proteins that influence early steps of T-cell commitment and development include, without limitation, those described in: Antica et al., Blood 84:111-117, 1994; Fine et al., Cellular Immunology 155:111-122, 1994; Galy et al., Blood 85:2770-2778, 1995; Toki et al., Proc. Nat. Acad Sci. USA 88:7548-7551, 1991.

Hematopoiesis Regulating Activity

A protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell

lines indicates involvement in regulating hematopoiesis, e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemias or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually treated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either *in-vivo* or *ex-vivo* (i.e., in conjunction with bone marrow transplantation or with peripheral progenitor cell transplantation (homologous or heterologous)) as normal cells or genetically manipulated for gene therapy.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for proliferation and differentiation of various hematopoietic lines are cited above.

Assays for embryonic stem cell differentiation (which will identify, among others, proteins that influence embryonic differentiation hematopoiesis) include, without limitation, those described in: Johansson et al. Cellular Biology 15:141-151, 1995; Keller et al., Molecular and Cellular Biology 13:473-486, 1993; McClanahan et al., Blood 81:2903-2915, 1993.

Assays for stem cell survival and differentiation (which will identify, among others, proteins that regulate lympho-hematopoiesis) include, without limitation, those described in: Methylcellulose colony forming assays, Freshney, M.G. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 265-268, Wiley-Liss, Inc., New York, NY. 1994; Hirayama et al., Proc. Natl. Acad. Sci. USA 89:5907-5911, 1992; Primitive hematopoietic colony forming cells with high proliferative potential, McNiece, I.K. and

Briddell, R.A. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 23-39, Wiley-Liss, Inc., New York, NY. 1994; Neben et al., Experimental Hematology 22:353-359, 1994; Cobblestone area forming cell assay, Ploemacher, R.E. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 1-21, Wiley-Liss, Inc.., New York, NY. 1994; Long term bone marrow cultures in the presence of stromal cells, Spooncer, E., Dexter, M. and Allen, T. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 163-179, Wiley-Liss, Inc., New York, NY. 1994; Long term culture initiating cell assay, Sutherland, H.J. In *Culture of Hematopoietic Cells*. R.I. Freshney, *et al.* eds. Vol pp. 139-162, Wiley-Liss, Inc., New York, NY. 1994.

Tissue Growth Activity

A protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair and replacement, and in the treatment of burns, incisions and ulcers.

A protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, has application in the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing a protein of the invention may have prophylactic use in closed as well as open fracture reduction and also in the improved fixation of artificial joints. *De novo* bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

A protein of this invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. A protein of the invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteoclast activity, etc.) mediated by inflammatory processes.

Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. A protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in

circumstances where such tissue is not normally formed, has application in the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing a tendon/ligament-like tissue inducing protein may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon/ligament cells or progenitors *ex vivo* for return *in vivo* to effect tissue repair. The compositions of the invention may also be useful in the treatment of tendinitis, carpal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue, *i.e.* for the treatment of central and peripheral nervous system diseases and neuropathies, as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, a protein may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the present invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using a protein of the invention.

Proteins of the invention may also be useful to promote better or faster closure of non-healing wounds, including without limitation pressure ulcers, ulcers associated with vascular insufficiency, surgical and traumatic wounds, and the like.

It is expected that a protein of the present invention may also exhibit activity for generation or regeneration of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the growth of cells comprising such tissues. Part of the desired effects may be by inhibition or modulation of fibrotic scarring to allow normal tissue to regenerate. A protein of the invention may also exhibit angiogenic activity.

A protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

A protein of the present invention may also be useful for promoting or inhibiting differentiation of tissues described above from precursor tissues or cells; or for inhibiting the growth of tissues described above.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for tissue generation activity include, without limitation, those described in: International Patent Publication No. WO95/16035 (bone, cartilage, tendon); International Patent Publication No. WO95/05846 (nerve, neuronal); International Patent Publication No. WO91/07491 (skin, endothelium).

Assays for wound healing activity include, without limitation, those described in: Winter, Epidermal Wound Healing, pps. 71-112 (Maibach, HI and Rovee, DT, eds.), Year Book Medical Publishers, Inc., Chicago, as modified by Eaglstein and Mertz, J. Invest. Dermatol 71:382-84 (1978).

Activin/Inhibin Activity

A protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins and are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, a protein of the present invention, alone or in heterodimers with a member of the inhibin α family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals. Alternatively, the protein of the invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-

β group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary. See, for example, United States Patent 4,798,885. A protein of the invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for activin/inhibin activity include, without limitation, those described in: Vale et al., Endocrinology 91:562-572, 1972; Ling et al., Nature 321:779-782, 1986; Vale et al., Nature 321:776-779, 1986; Mason et al., Nature 318:659-663, 1985; Forage et al., Proc. Natl. Acad. Sci. USA 83:3091-3095, 1986.

Chemotactic/Chemokinetic Activity

A protein of the present invention may have chemotactic or chemokinetic activity (e.g., act as a chemokine) for mammalian cells, including, for example, monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

A protein or peptide has chemotactic activity for a particular cell population if it can stimulate, directly or indirectly, the directed orientation or movement of such cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assays for chemotactic activity (which will identify proteins that induce or prevent chemotaxis) consist of assays that measure the ability of a protein to induce the migration of cells across a membrane as well as the ability of a protein to induce the adhesion of one cell population to another cell population. Suitable assays for movement and adhesion

include, without limitation, those described in: Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 6.12, Measurement of alpha and beta Chemokines 6.12.1-6.12.28; Taub et al. J. Clin. Invest. 95:1370-1376, 1995; Lind et al. APMIS 103:140-146, 1995; Muller et al Eur. J. Immunol. 25: 1744-1748; Gruber et al. J. of Immunol. 152:5860-5867, 1994; Johnston et al. J. of Immunol. 153: 1762-1768, 1994.

Hemostatic and Thrombolytic Activity

A protein of the invention may also exhibit hemostatic or thrombolytic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom (such as, for example, infarction of cardiac and central nervous system vessels (e.g., stroke).

The activity of a protein of the invention may, among other means, be measured by the following methods:

Assay for hemostatic and thrombolytic activity include, without limitation, those described in: Linet et al., J. Clin. Pharmacol. 26:131-140, 1986; Burdick et al., Thrombosis Res. 45:413-419, 1987; Humphrey et al., Fibrinolysis 5:71-79 (1991); Schaub, Prostaglandins 35:467-474, 1988.

Receptor/Ligand Activity

A protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including without limitation, cellular adhesion molecules (such as selectins, integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses). Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. A protein of the present invention (including, without

limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

The activity of a protein of the invention may, among other means, be measured by the following methods:

Suitable assays for receptor-ligand activity include without limitation those described in:Current Protocols in Immunology, Ed by J.E. Coligan, A.M. Kruisbeek, D.H. Margulies, E.M. Shevach, W.Strober, Pub. Greene Publishing Associates and Wiley-Interscience (Chapter 7.28, Measurement of Cellular Adhesion under static conditions 7.28.1-7.28.22), Takai et al., Proc. Natl. Acad. Sci. USA 84:6864-6868, 1987; Bierer et al., J. Exp. Med. 168:1145-1156, 1988; Rosenstein et al., J. Exp. Med. 169:149-160 1989; Stoltenborg et al., J. Immunol. Methods 175:59-68, 1994; Stitt et al., Cell 80:661-670, 1995.

Anti-Inflammatory Activity

Proteins of the present invention may also exhibit anti-inflammatory activity. The anti-inflammatory activity may be achieved by providing a stimulus to cells involved in the inflammatory response, by inhibiting or promoting cell-cell interactions (such as, for example, cell adhesion), by inhibiting or promoting chemotaxis of cells involved in the inflammatory process, inhibiting or promoting cell extravasation, or by stimulating or suppressing production of other factors which more directly inhibit or promote an inflammatory response. Proteins exhibiting such activities can be used to treat inflammatory conditions including chronic or acute conditions), including without limitation inflammation associated with infection (such as septic shock, sepsis or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine-induced lung injury, inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-1. Proteins of the invention may also be useful to treat anaphylaxis and hypersensitivity to an antigenic substance or material.

Cadherin/Tumor Invasion Suppressor Activity

Cadherins are calcium-dependent adhesion molecules that appear to play major roles during development, particularly in defining specific cell types. Loss or alteration of normal cadherin expression can lead to changes in cell adhesion properties linked to tumor growth and metastasis. Cadherin malfunction is also implicated in other human

diseases, such as pemphigus vulgaris and pemphigus foliaceus (auto-immune blistering skin diseases), Crohn's disease, and some developmental abnormalities.

The cadherin superfamily includes well over forty members, each with a distinct pattern of expression. All members of the superfamily have in common conserved extracellular repeats (cadherin domains), but structural differences are found in other parts of the molecule. The cadherin domains bind calcium to form their tertiary structure and thus calcium is required to mediate their adhesion. Only a few amino acids in the first cadherin domain provide the basis for homophilic adhesion; modification of this recognition site can change the specificity of a cadherin so that instead of recognizing only itself, the mutant molecule can now also bind to a different cadherin. In addition, some cadherins engage in heterophilic adhesion with other cadherins.

E-cadherin, one member of the cadherin superfamily, is expressed in epithelial cell types. Pathologically, if E-cadherin expression is lost in a tumor, the malignant cells become invasive and the cancer metastasizes. Transfection of cancer cell lines with polynucleotides expressing E-cadherin has reversed cancer-associated changes by returning altered cell shapes to normal, restoring cells' adhesiveness to each other and to their substrate, decreasing the cell growth rate, and drastically reducing anchorage-independent cell growth. Thus, reintroducing E-cadherin expression reverts carcinomas to a less advanced stage. It is likely that other cadherins have the same invasion suppressor role in carcinomas derived from other tissue types. Therefore, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be used to treat cancer. Introducing such proteins or polynucleotides into cancer cells can reduce or eliminate the cancerous changes observed in these cells by providing normal cadherin expression.

Cancer cells have also been shown to express cadherins of a different tissue type than their origin, thus allowing these cells to invade and metastasize in a different tissue in the body. Proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can be substituted in these cells for the inappropriately expressed cadherins, restoring normal cell adhesive properties and reducing or eliminating the tendency of the cells to metastasize.

Additionally, proteins of the present invention with cadherin activity, and polynucleotides of the present invention encoding such proteins, can used to generate antibodies recognizing and binding to cadherins. Such antibodies can be used to block the adhesion of inappropriately expressed tumor-cell cadherins, preventing the cells from

forming a tumor elsewhere. Such an anti-cadherin antibody can also be used as a marker for the grade, pathological type, and prognosis of a cancer, i.e. the more progressed the cancer, the less cadherin expression there will be, and this decrease in cadherin expression can be detected by the use of a cadherin-binding antibody.

Fragments of proteins of the present invention with cadherin activity, preferably a polypeptide comprising a decapeptide of the cadherin recognition site, and polynucleotides of the present invention encoding such protein fragments, can also be used to block cadherin function by binding to cadherins and preventing them from binding in ways that produce undesirable effects. Additionally, fragments of proteins of the present invention with cadherin activity, preferably truncated soluble cadherin fragments which have been found to be stable in the circulation of cancer patients, and polynucleotides encoding such protein fragments, can be used to disturb proper cell-cell adhesion.

Assays for cadherin adhesive and invasive suppressor activity include, without limitation, those described in: Hortsch et al. J Biol Chem 270 (32): 18809-18817, 1995; Miyaki et al. Oncogene 11: 2547-2552, 1995; Ozawa et al. Cell 63: 1033-1038, 1990.

Tumor Inhibition Activity

In addition to the activities described above for immunological treatment or prevention of tumors, a protein of the invention may exhibit other anti-tumor activities. A protein may inhibit tumor growth directly or indirectly (such as, for example, via ADCC). A protein may exhibit its tumor inhibitory activity by acting on tumor tissue or tumor precursor tissue, by inhibiting formation of tissues necessary to support tumor growth (such as, for example, by inhibiting angiogenesis), by causing production of other factors, agents or cell types which inhibit tumor growth, or by suppressing, eliminating or inhibiting factors, agents or cell types which promote tumor growth.

Other Activities

A protein of the invention may also exhibit one or more of the following additional activities or effects: inhibiting the growth, infection or function of, or killing, infectious agents, including, without limitation, bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) bodily characteristics, including, without limitation, height, weight, hair color, eye color, skin, fat to lean ratio or other tissue pigmentation, or organ or body part size or shape (such as, for example, breast augmentation or diminution, change in bone form or shape); effecting biorhythms or caricadic cycles or rhythms;

effecting the fertility of male or female subjects; effecting the metabolism, catabolism, anabolism, processing, utilization, storage or elimination of dietary fat, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional factors or component(s); effecting behavioral characteristics, including, without limitation, appetite, libido, stress, cognition (including cognitive disorders), depression (including depressive disorders) and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; hormonal or endocrine activity; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases; treatment of hyperproliferative disorders (such as, for example, psoriasis); immunoglobulin-like activity (such as, for example, the ability to bind antigens or complement); and the ability to act as an antigen in a vaccine composition to raise an immune response against such protein or another material or entity which is cross-reactive with such protein.

ADMINISTRATION AND DOSING

A protein of the present invention (from whatever source derived, including without limitation from recombinant and non-recombinant sources) may be used in a pharmaceutical composition when combined with a pharmaceutically acceptable carrier. Such a composition may also contain (in addition to protein and a carrier) diluents, fillers, salts, buffers, stabilizers, solubilizers, and other materials well known in the art. The term "pharmaceutically acceptable" means a non-toxic material that does not interfere with the effectiveness of the biological activity of the active ingredient(s). The characteristics of the carrier will depend on the route of administration. The pharmaceutical composition of the invention may also contain cytokines, lymphokines, or other hematopoietic factors such as M-CSF, GM-CSF, TNF, IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IFN, TNF0, TNF1, TNF2, G-CSF, Meg-CSF, thrombopoietin, stem cell factor, and erythropoietin. The pharmaceutical composition may further contain other agents which either enhance the activity of the protein or compliment its activity or use in treatment. Such additional factors and/or agents may be included in the pharmaceutical composition to produce a synergistic effect with protein of the invention, or to minimize side effects. Conversely, protein of the present invention may be included in formulations of the particular cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent to minimize side effects

of the cytokine, lymphokine, other hematopoietic factor, thrombolytic or anti-thrombotic factor, or anti-inflammatory agent.

A protein of the present invention may be active in multimers (e.g., heterodimers or homodimers) or complexes with itself or other proteins. As a result, pharmaceutical compositions of the invention may comprise a protein of the invention in such multimeric or complexed form.

The pharmaceutical composition of the invention may be in the form of a complex of the protein(s) of present invention along with protein or peptide antigens. The protein and/or peptide antigen will deliver a stimulatory signal to both B and T lymphocytes. B lymphocytes will respond to antigen through their surface immunoglobulin receptor. T lymphocytes will respond to antigen through the T cell receptor (TCR) following presentation of the antigen by MHC proteins. MHC and structurally related proteins including those encoded by class I and class II MHC genes on host cells will serve to present the peptide antigen(s) to T lymphocytes. The antigen components could also be supplied as purified MHC-peptide complexes alone or with co-stimulatory molecules that can directly signal T cells. Alternatively antibodies able to bind surface immunolgobulin and other molecules on B cells as well as antibodies able to bind the TCR and other molecules on T cells can be combined with the pharmaceutical composition of the invention.

The pharmaceutical composition of the invention may be in the form of a liposome in which protein of the present invention is combined, in addition to other pharmaceutically acceptable carriers, with amphipathic agents such as lipids which exist in aggregated form as micelles, insoluble monolayers, liquid crystals, or lamellar layers in aqueous solution. Suitable lipids for liposomal formulation include, without limitation, monoglycerides, diglycerides, sulfatides, lysolecithin, phospholipids, saponin, bile acids, and the like. Preparation of such liposomal formulations is within the level of skill in the art, as disclosed, for example, in U.S. Patent No. 4,235,871; U.S. Patent No. 4,501,728; U.S. Patent No. 4,837,028; and U.S. Patent No. 4,737,323, all of which are incorporated herein by reference.

As used herein, the term "therapeutically effective amount" means the total amount of each active component of the pharmaceutical composition or method that is sufficient to show a meaningful patient benefit, i.e., treatment, healing, prevention or amelioration of the relevant medical condition, or an increase in rate of treatment, healing, prevention or amelioration of such conditions. When applied to an individual active

ingredient, administered alone, the term refers to that ingredient alone. When applied to a combination, the term refers to combined amounts of the active ingredients that result in the therapeutic effect, whether administered in combination, serially or simultaneously.

In practicing the method of treatment or use of the present invention, a therapeutically effective amount of protein of the present invention is administered to a mammal having a condition to be treated. Protein of the present invention may be administered in accordance with the method of the invention either alone or in combination with other therapies such as treatments employing cytokines, lymphokines or other hematopoietic factors. When co-administered with one or more cytokines, lymphokines or other hematopoietic factors, protein of the present invention may be administered either simultaneously with the cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors, or sequentially. If administered sequentially, the attending physician will decide on the appropriate sequence of administering protein of the present invention in combination with cytokine(s), lymphokine(s), other hematopoietic factor(s), thrombolytic or anti-thrombotic factors.

Administration of protein of the present invention used in the pharmaceutical composition or to practice the method of the present invention can be carried out in a variety of conventional ways, such as oral ingestion, inhalation, topical application or cutaneous; subcutaneous, intraperitoneal, parenteral or intravenous injection. Intravenous administration to the patient is preferred.

When a therapeutically effective amount of protein of the present invention is administered orally, protein of the present invention will be in the form of a tablet, capsule, powder, solution or elixir. When administered in tablet form, the pharmaceutical composition of the invention may additionally contain a solid carrier such as a gelatin or an adjuvant. The tablet, capsule, and powder contain from about 5 to 95% protein of the present invention, and preferably from about 25 to 90% protein of the present invention. When administered in liquid form, a liquid carrier such as water, petroleum, oils of animal or plant origin such as peanut oil, mineral oil, soybean oil, or sesame oil, or synthetic oils may be added. The liquid form of the pharmaceutical composition may further contain physiological saline solution, dextrose or other saccharide solution, or glycols such as ethylene glycol, propylene glycol or polyethylene glycol. When administered in liquid form, the pharmaceutical composition contains from about 0.5 to 90% by weight of protein

of the present invention, and preferably from about 1 to 50% protein of the present invention.

When a therapeutically effective amount of protein of the present invention is administered by intravenous, cutaneous or subcutaneous injection, protein of the present invention will be in the form of a pyrogen-free, parenterally acceptable aqueous solution. The preparation of such parenterally acceptable protein solutions, having due regard to pH, isotonicity, stability, and the like, is within the skill in the art. A preferred pharmaceutical composition for intravenous, cutaneous, or subcutaneous injection should contain, in addition to protein of the present invention, an isotonic vehicle such as Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, Lactated Ringer's Injection, or other vehicle as known in the art. The pharmaceutical composition of the present invention may also contain stabilizers, preservatives, buffers, antioxidants, or other additives known to those of skill in the art.

The amount of protein of the present invention in the pharmaceutical composition of the present invention will depend upon the nature and severity of the condition being treated, and on the nature of prior treatments which the patient has undergone. Ultimately, the attending physician will decide the amount of protein of the present invention with which to treat each individual patient. Initially, the attending physician will administer low doses of protein of the present invention and observe the patient's response. Larger doses of protein of the present invention may be administered until the optimal therapeutic effect is obtained for the patient, and at that point the dosage is not increased further. It is contemplated that the various pharmaceutical compositions used to practice the method of the present invention should contain about 0.01 µg to about 100 mg (preferably about 0.1ng to about 10 mg, more preferably about 0.1 µg to about 1 mg) of protein of the present invention per kg body weight.

The duration of intravenous therapy using the pharmaceutical composition of the present invention will vary, depending on the severity of the disease being treated and the condition and potential idiosyncratic response of each individual patient. It is contemplated that the duration of each application of the protein of the present invention will be in the range of 12 to 24 hours of continuous intravenous administration. Ultimately the attending physician will decide on the appropriate duration of intravenous therapy using the pharmaceutical composition of the present invention.

Protein of the invention may also be used to immunize animals to obtain polyclonal and monoclonal antibodies which specifically react with the protein. Such

antibodies may be obtained using either the entire protein or fragments thereof as an immunogen. The peptide immunogens additionally may contain a cysteine residue at the carboxyl terminus, and are conjugated to a hapten such as keyhole limpet hemocyanin (KLH). Methods for synthesizing such peptides are known in the art, for example, as in R.P. Merrifield, J. Amer.Chem.Soc. 85, 2149-2154 (1963); J.L. Krstenansky, *et al.*, FEBS Lett. 211, 10 (1987). Monoclonal antibodies binding to the protein of the invention may be useful diagnostic agents for the immunodetection of the protein. Neutralizing monoclonal antibodies binding to the protein may also be useful therapeutics for both conditions associated with the protein and also in the treatment of some forms of cancer where abnormal expression of the protein is involved. In the case of cancerous cells or leukemic cells, neutralizing monoclonal antibodies against the protein may be useful in detecting and preventing the metastatic spread of the cancerous cells, which may be mediated by the protein.

For compositions of the present invention which are useful for bone, cartilage, tendon or ligament regeneration, the therapeutic method includes administering the composition topically, systematically, or locally as an implant or device. When administered, the therapeutic composition for use in this invention is, of course, in a pyrogen-free, physiologically acceptable form. Further, the composition may desirably be encapsulated or injected in a viscous form for delivery to the site of bone, cartilage or tissue damage. Topical administration may be suitable for wound healing and tissue repair. Therapeutically useful agents other than a protein of the invention which may also optionally be included in the composition as described above, may alternatively or additionally, be administered simultaneously or sequentially with the composition in the methods of the invention. Preferably for bone and/or cartilage formation, the composition would include a matrix capable of delivering the protein-containing composition to the site of bone and/or cartilage damage, providing a structure for the developing bone and cartilage and optimally capable of being resorbed into the body. Such matrices may be formed of materials presently in use for other implanted medical applications.

The choice of matrix material is based on biocompatibility, biodegradability, mechanical properties, cosmetic appearance and interface properties. The particular application of the compositions will define the appropriate formulation. Potential matrices for the compositions may be biodegradable and chemically defined calcium sulfate, tricalciumphosphate, hydroxyapatite, polylactic acid, polyglycolic acid and

polyanhydrides. Other potential materials are biodegradable and biologically well-defined, such as bone or dermal collagen. Further matrices are comprised of pure proteins or extracellular matrix components. Other potential matrices are nonbiodegradable and chemically defined, such as sintered hydroxapatite, bioglass, aluminates, or other ceramics. Matrices may be comprised of combinations of any of the above mentioned types of material, such as polylactic acid and hydroxyapatite or collagen and tricalciumphosphate. The bioceramics may be altered in composition, such as in calcium-aluminate-phosphate and processing to alter pore size, particle size, particle shape, and biodegradability.

Presently preferred is a 50:50 (mole weight) copolymer of lactic acid and glycolic acid in the form of porous particles having diameters ranging from 150 to 800 microns. In some applications, it will be useful to utilize a sequestering agent, such as carboxymethyl cellulose or autologous blood clot, to prevent the protein compositions from disassociating from the matrix.

A preferred family of sequestering agents is cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), including methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose, the most preferred being cationic salts of carboxymethylcellulose (CMC). Other preferred sequestering agents include hyaluronic acid, sodium alginate, poly(ethylene glycol), polyoxyethylene oxide, carboxyvinyl polymer and poly(vinyl alcohol). The amount of sequestering agent useful herein is 0.5-20 wt%, preferably 1-10 wt% based on total formulation weight, which represents the amount necessary to prevent desorbtion of the protein from the polymer matrix and to provide appropriate handling of the composition, yet not so much that the progenitor cells are prevented from infiltrating the matrix, thereby providing the protein the opportunity to assist the osteogenic activity of the progenitor cells.

In further compositions, proteins of the invention may be combined with other agents beneficial to the treatment of the bone and/or cartilage defect, wound, or tissue in question. These agents include various growth factors such as epidermal growth factor (EGF), platelet derived growth factor (PDGF), transforming growth factors (TGF-α and TGF-β), and insulin-like growth factor (IGF).

The therapeutic compositions are also presently valuable for veterinary applications. Particularly domestic animals and thoroughbred horses, in addition to humans, are desired patients for such treatment with proteins of the present invention.

The dosage regimen of a protein-containing pharmaceutical composition to be used in tissue regeneration will be determined by the attending physician considering various factors which modify the action of the proteins, e.g., amount of tissue weight desired to be formed, the site of damage, the condition of the damaged tissue, the size of a wound, type of damaged tissue (e.g., bone), the patient's age, sex, and diet, the severity of any infection, time of administration and other clinical factors. The dosage may vary with the type of matrix used in the reconstitution and with inclusion of other proteins in the pharmaceutical composition. For example, the addition of other known growth factors, such as IGF I (insulin like growth factor I), to the final composition, may also effect the dosage. Progress can be monitored by periodic assessment of tissue/bone growth and/or repair, for example, X-rays, histomorphometric determinations and tetracycline labeling.

Polynucleotides of the present invention can also be used for gene therapy. Such polynucleotides can be introduced either *in vivo* or *ex vivo* into cells for expression in a mammalian subject. Polynucleotides of the invention may also be administered by other known methods for introduction of nucleic acid into a cell or organism (including, without limitation, in the form of viral vectors or naked DNA).

Cells may also be cultured *ex vivo* in the presence of proteins of the present invention in order to proliferate or to produce a desired effect on or activity in such cells. Treated cells can then be introduced *in vivo* for therapeutic purposes.

Patent and literature references cited herein are incorporated by reference as if fully set forth.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Jacobs, Kenneth
McCoy, John M.
LaVallie, Edward R.
Racie, Lisa A.
Merberg, David
Treacy, Maurice
Spaulding, Vikki
Agostino, Michael J.

(ii) TITLE OF INVENTION: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(iii) NUMBER OF SEQUENCES: 33

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Genetics Institute, Inc.
(B) STREET: 87 CambridgePark Drive
(C) CITY: Cambridge
(D) STATE: MA
(E) COUNTRY: U.S.A.
(F) ZIP: 02140

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER:
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(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Sprunger, Suzanne A.
(B) REGISTRATION NUMBER: 41,323

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (617) 498-8284
(B) TELEFAX: (617) 876-5851

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1433 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GCCCGTGGTT ACACAGCTAA TAGGTGGTGG AGATGGAGAC AGAATTCAAA CCCAGGCATT 60

CTTGATCTAC AGTATACACT CTTACCCACC ATCCTACACA GCCTTTCTTA TTCATAAAAT 120

ATTTTCTACA GTGCAAGAAA ATTTTGATAG CTTGCTTATT TATTCAAGAT TTAGACTATA 180

TAGATTAACT AGACTATCAA GATTTTAAAT TCTTGTGTTT TTTGTTTTTY YCCCCCTCTG 240

TGGCATAACT ATCTCTTAGT GATTTGAAGT TCTGATAGGC ATTTATTTAT GTTTTTGATT 300

AATTAAAAAA AGGGAAAAAA ATGGAACATA ATTATTGAAG CTATCGTCTA GGTAAAAACC 360

TTTCTAAATG TAAGGTTCAT TTAGATTGAT GACCTGTAGA GTGTAACAGT ATTGCCATAG 420

GCATACAGCT TTTTAATCAC ATATCATACA TAAACAAATT AGTAATACAG GTGGGTAGAT 480

ACAGACCCTA ACTTTGAGCT CTAAGATGAA ATTTGTTTAT AAATCCCTAG TTTCCATTCA 540

GTTTTTTCAA TATTTATCAA ACACCTACTG TGCCAGGCAT TGTTTAGGCA CAGGGGATAC 600

AGCAGGAGAA CAAAATGAAC AAAATTTTTT GCCTTCACAG AGCTAATTTT TTGTATTTTT 660

TTGTAGAGAT GGGGTTTTGC CATGTTTGCC AGTCTGGTCT CAACCTCCTA AGCTCAAGCA 720

GCCCACCCTC CTTGGCTTCC CAAAGTGCTG AGATTACAGG CATGAGCCAC CGCACTCTTC 780

TTAGCTATTT TTCATAGAAA CTTTATGTAT AAAAATAGAA GGGTAATGAC ACACCACCTT 840

TCTACTGATC TCCCCACTTC AGTAGTTATC ACATAACAGT CTTTTTTCAC CTATCTCCTT 900

CACTTTACCT CCTCTCCCTT AGTACTTTGA AGTAAATCTC AATGCAAGCT GGTATGTTTT 960

TCAAAATGAA ACATATAAAC ATGGACTAGA AAAAAATCTC TTCATACAGG ATTTGGTTTT 1020

GCAGAGAATT TACAAAGTGC GGTTAATGTA TGCCAATGGT TTCTCAGTTT GGATATCGAG 1080

ATCCTTAGAT GGACCATGAA GCTGGTAATA ATTTTATAGC TAACTTTTGT TAAGTGCTTA 1140

CTATATGCCA GGCACTGTTC TAAGCATTTT ACGTGTATTC ATTCATTCAG TTCTCACAAC 1200

TCTTTTAATT AGGTATTATT ATGATCTCCA TCTCAAAACA AAACAAAACA AAAAAATTAG 1260

CCTGGCATGG TGGCAGGCGC CTGTAATCCC AGTTACTTGA GAGGCTAAGG CAGGAGAATC 1320

GCTTGAATCT GGGAGGCAGA GGTTGCAGTG AGCCGAGATT GCACTACTGC ACTCCAGCCT 1380

GGGTGACAGA ATGAGACTCT GTCTCAAAAA AAAAAAAAAA AAAAAAAAAA AAA 1433

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

Met Lys Phe Val Tyr Lys Ser Leu Val Ser Ile Gln Phe Phe Gln Tyr
1 5 10 15

Leu Ser Asn Thr Tyr Cys Ala Arg His Cys Leu Gly Thr Gly Asp Thr
20 25 30

Ala Gly Glu Gln Asn Glu Gln Asn Phe Leu Pro Ser Gln Ser
35 40 45

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1401 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

TCGGGACAGA TTTAAGTGCA GCGTGGATTT TTTTTTTCTC ACTTTGCCTT GTGTTTTCCA 60

CCCTGAAAGA ATGTTGTGGC TGCTCTTTTT TCTGGTGACT GCCATTCATG CTGAACTCTG 120

TCAACCAGGT GCAGAAAATG CTTTTAAAGT GAGACTTAGT ATCAGAACAG CTCTGGGAGA 180

TAAAGCATAT GCCTGGGATA CCAATGAAGA ATACCTCTTC AAAGCGATGG TAGCTTTCTC 240

CATGAGAAAA GTTCCCAACA GAGAAGCAAC AGAAATTTCC CATGTCCTAC TTTGCAATGT 300

AACCCAGAGG GTATCATTCT GGTTTGTGGT TACAGACCCT TCAAAAAATC ACACCCTTCC 360

TGCTGTTGAG GTGCAATCAG CCATAAGAAT GAACAAGAAC CGGATCAACA ATGCCTTCTT 420

TGTAAATGAC CAAACTCTGG AATTTTTAAA AATCCCTTCC ACACTTGCAC CACCCATGGA 480

CCCATCTGTG CCCATCTGGA TTATTATATT TGGTGTGATA TTTTGCATCA TCATAGTTGC 540

AATTGCACTA CTGATTTTAT CAGGGATCTG GCAACGTAGA AGAAAGAACA AAGAACCATC 600

TGAAGTGGAT GACGCTGAAG ATAAGTGTGA AAACATGATC ACAATTGAAA ATGGCATCCC 660

CTCTGATCCC CTGGACATGA AGGGAGGGCA TATTAATGAT GCCTTCATGA CAGAGGATGA 720

GAGGCTCACC CCTCTCTGAA GGGCTGTTGT TCTGCTTCCT CAAGAAATTA AACATTTGTT 780

TCTGTGTGAC TGCTGAGCAT CCTGAAATAC CAAGAGCAGA TCATATATTT TGTTTCACCA 840

TTCTTCTTTT GTAATAAATT TTGAATGTGC TTGAAAGTGA AAAGCAATCA ATTATACCCA 900

CCAACACCAC TGAAATCATA AGCTATTCAC GACTCAAAAT ATTCTAAAAT ATTTTTCTGA 960

CAGTATAGTG TATAAATGTG GTCATGTGGT ATTTGTAGTT ATTGATTTAA GCATTTTTAG 1020

AAATAAGATC AGGCATATGT ATATATTTTC ACACTTCAAA GACCTAAGGA AAAATAAATT 1080

TTCCAGTGGA GAATACATAT AATATGGTGT AGAAATCATT GAAAATGGAT CCTTTTTGAC 1140

GATCACTTAT ATCACTCTGT ATATGACTAA GTAAACAAAA GTGAGAAGTA ATTATTGTAA 1200

ATGGATGGAT AAAAATGGAA TTACTCATAT ACAGGGTGGA ATTTTATCCT GTTATCACAC 1260

CAACAGTTGA TTATATATTT TCTGAATATC AGCCCCTAAT AGGACAATTC TATTTGTTGA 1320

CCATTTCTAC AATTTGTAAA AGTCCAATCT GTGCTAACTT AATAAAGTAA TAATCATCTC 1380

TTTTAAAAAA AAAAAAAAAA A 1401

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 222 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Met Leu Trp Leu Leu Phe Phe Leu Val Thr Ala Ile His Ala Glu Leu
1 5 10 15

Cys Gln Pro Gly Ala Glu Asn Ala Phe Lys Val Arg Leu Ser Ile Arg
20 25 30

Thr Ala Leu Gly Asp Lys Ala Tyr Ala Trp Asp Thr Asn Glu Glu Tyr
35 40 45

Leu Phe Lys Ala Met Val Ala Phe Ser Met Arg Lys Val Pro Asn Arg
50 55 60

Glu Ala Thr Glu Ile Ser His Val Leu Leu Cys Asn Val Thr Gln Arg
65 70 75 80

Val Ser Phe Trp Phe Val Val Thr Asp Pro Ser Lys Asn His Thr Leu
85 90 95

Pro Ala Val Glu Val Gln Ser Ala Ile Arg Met Asn Lys Asn Arg Ile
100 105 110

Asn Asn Ala Phe Phe Val Asn Asp Gln Thr Leu Glu Phe Leu Lys Ile
115 120 125

Pro Ser Thr Leu Ala Pro Pro Met Asp Pro Ser Val Pro Ile Trp Ile
130 135 140

Ile Ile Phe Gly Val Ile Phe Cys Ile Ile Ile Val Ala Ile Ala Leu
145 150 155 160

Leu Ile Leu Ser Gly Ile Trp Gln Arg Arg Arg Lys Asn Lys Glu Pro
165 170 175

Ser Glu Val Asp Asp Ala Glu Asp Lys Cys Glu Asn Met Ile Thr Ile
180 185 190

Glu Asn Gly Ile Pro Ser Asp Pro Leu Asp Met Lys Gly Gly His Ile
195 200 205

Asn Asp Ala Phe Met Thr Glu Asp Glu Arg Leu Thr Pro Leu
210 215 220

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 441 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

GCGGCCGCAG GTCTAGAATT CAATCGGCCA CAAGCTACTC TTTGGAGCCC ATCTATGGTT 60

TGTGGTATGA CCACTCCTCC AACTTCTCCT GGAAATGTCC CACCTGATCT GTCACACCCT 120

TACAGTAAAG TCTTTGGTAC AACTGCAGGT GGAAAAGGAA CTCCTCTGGG AACCCCAGCA 180

ACCTCTCCTC CTCCAGCCCC ACTCTGTCAT TCGGATGACT ACGTGCACAT TTCACTCCCC 240

CAGGCCACAG TCACACCCCC CAGGAAGGAA GAGAGAATGG ATTCTGCAAG ACCATGTCTA 300

CACAGACAAC ACCATCTTCT GAATGACAGA GGATCAGAAG AGCCACCTGG CAGCAAAGGT 360

TCTGTCACTC TAAGTGATCT TCCAGGGTTT TTAGGTGATC TGGCCTCTGA AGAAGATAGT 420

ATTGAAAAAA AAAAAAAAAA A 441

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 123 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Met Val Cys Gly Met Thr Thr Pro Pro Thr Ser Pro Gly Asn Val Pro
1 5 10 15

Pro Asp Leu Ser His Pro Tyr Ser Lys Val Phe Gly Thr Thr Ala Gly
20 25 30

Gly Lys Gly Thr Pro Leu Gly Thr Pro Ala Thr Ser Pro Pro Pro Ala
35 40 45

Pro Leu Cys His Ser Asp Asp Tyr Val His Ile Ser Leu Pro Gln Ala
50 55 60

Thr Val Thr Pro Pro Arg Lys Glu Glu Arg Met Asp Ser Ala Arg Pro
65 70 75 80

Cys Leu His Arg Gln His His Leu Leu Asn Asp Arg Gly Ser Glu Glu
85 90 95

Pro Pro Gly Ser Lys Gly Ser Val Thr Leu Ser Asp Leu Pro Gly Phe
100 105 110

Leu Gly Asp Leu Ala Ser Glu Glu Asp Ser Ile
115 120

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2353 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

AAGAAGGCGA TGTCACTATT GGAGAAGATG CACCAAATCT TTCTTTTAGC ACCAGTGTGG 60

GAAATGAGGA CGCCAGGACA GCCTGGCCCG AATTACAACA GAGCCATGCT GTTAATCAGC 120

TCAAAGATTT GTTGCGCCAA CAAGCAGATA AGGAAAGTGA AGTATCTCCG TCAAGAAGAA 180

GAAAAATGTC CCCCTTGAGG TCATTAGAAC ATGAGGAAAC CAATATGCCT ACTATGCACG 240

ACCTTGTTCA TACTATTAAT GACCAGTCTC AATATATTCA TCATTTAGAG GCAGAAGTTA 300

AGTTCTGCAA GGAGGAACTC TCTGGAATGA AAAATAAAAT ACAAGTAGTT GTGCTTGAAA 360

ACGAAGGGCT CCAGCAACAG CTAAAATCTC AAAGACAAGA GGAGACACTG AGGGAACAAA 420

CACTTCTGGA TGCATCCGGA AACATGCACA ATTCTTGGAT TACAACAGGT GAAGATTCTG 480

GGGTGGGCGA AACCTCCAAA AGACCATTTT CCCATGACAA TGCAGATTTT GGCAAAGCTG 540

CATCTGCTGG TGAGCAGCTA GAACTGGAGA AGCTAAAACT TACTTATGAG GAAAAGTGTG 600

AAATTGAGGA ATCCCAATTG AAGTTTTTGA GGAACGACTT AGCTGAATAT CAGAGAACTT 660

GTGAAGATCT TAAAGAGCAA CTAAAGCATA AAGAATTTCT TCTGGCTGCT AATACTTGTA 720

ACCGTGTTGG TGGTCTTTGT TTGAAATGTG CTCAGCATGA AGCTGTTCTT TCCCAAACCC 780

ATACTAATGT TCATATGCAG ACCATCGAAA GACTGGTTAA AGAAAGAGAT GACTTGATGT 840

CTGCACTAGT TTCCGTAAGG AGCAGCTTGG CAGATACGCA GCAAAGAGAA GCAAGTGCTT 900

ATGAACAGGT GAAACAAGTT TTGCAAATAT CTGAGGAAGC CAATTTTGAA AAAACCAAGG 960

CTTTAATCCA GTGTGACCAG TTGAGGAAGG AGCTGGAGAG GCAGGCGGAG CGACTTGAAA 1020

AAGAACTTGC ATCTCAGCAA GAGAAAAGGG CCATTGAGAA AGACATGATG AAAAAGGAAA 1080

TAACGAAAGA AAGGGAGTAC ATGGGATCAA AGATGTTGAT CTTGTCTCAG AATATTGCCC 1140

AACTGGAGGC CCAGGTGGAA AAGGTTACAA AGGAAAAGAT TTCAGCTATT AATCAACTGG 1200

AGGAAATTCA AAGCCAGCTG GCTTCTCGGG AAATGGATGT CACAAAGGTG TGTGGAGAAA 1260

TGCGCTATCA GCTGAATAAA ACCAACATGG AGAAGGATGA GGCAGAAAAG GAGCACAGAG 1320

AGTTCAGAGC AAAAACTAAC AGGGATCTTG AAATTAAAGA TCAGGAAATA GAGAAATTGA 1380

GAATAGAACT GGATGAAAGC AAACAACACT TGGAACAGGA GCAGCAGAAG GCAGCCCTGG 1440

CCAGAGAGGA GTGCCTGAGA CTAACAGAAC TGCTGGGCGA ATCTGAGCAC CAACTGCACC 1500

TCACCAGACA GGAAAAAGAT AGCATTCAGC AGAGCTTTAG CAAGGAAGCA AAGGCCCAAG 1560

CCCTTCAGGC CCAGCAAAGA GAGCAGGAGC TGACACAGAA GATACAGCAA ATGGAAGCCC 1620

AGCATGACAA AACTGAAAAT GAACAGTATT TGTTGCTGAC CTCCCAGAAT ACATTTTTGA 1680

CAAAGTTAAA GGAAGAATGC TGTACATTAG CCAAGAAACT GGAACAAATC TCTCAAAAAA 1740

CCAGATCTGA AATAGCTCAA CTCAGTCAAG AAAAAAGGTA TACATATGAT AAATTGGGAA 1800

AGTTACAGAG AAGAAATGAA GAATTGGAGG AACAGTGTGT CCAGCATGGG AGAGTACATG 1860

AGACGATGAA GCAAAGGCTA AGGCAGCTGG ATAAGCACAG CCAGGCCACA GCCCAGCAGC 1920

TGGTGCAGCT CCTCAGCAAG CAGAACCAGC TTCTCCTGGA GAGGCAGAGC CTGTCGGAAG 1980

AGGTGGACCG GCTGCGGACC CAGTTACCCA GCATGCCACA ATCTGATTGC TGACCTGGAT 2040

GGAACAGAGT GAAATAAATG ATTTACAAAG AGATATTTAC ATTCATCTGG TTTAGACTTA 2100

ATATGCCACA ACGCACCACG ACCTTCCCAG GGTGACACCG CCTCAGCCTG CAGTGGGGCT 2160

GGTCCTCATC AACGCGGGCG CTGTCCCCGC ACGCAGTCGG GCTGGAGCTG GAGTCTGACT 2220

CTAGCTGAGC AGAGCTCCTG GTGTATGTTT TCAGAAATGG CTTGAAGTTA TGTGTTTAAA 2280

TCTGCTCATT CGTATGCTAG GTTATACATA TGATTTTCAA TAAATGAACT TTTTAAAGAA 2340

AAAAAAAAAA AAA 2353

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 615 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

Met Ser Pro Leu Arg Ser Leu Glu His Glu Glu Thr Asn Met Pro Thr
1 5 10 15

Met His Asp Leu Val His Thr Ile Asn Asp Gln Ser Gln Tyr Ile His
20 25 30

His Leu Glu Ala Glu Val Lys Phe Cys Lys Glu Glu Leu Ser Gly Met
35 40 45

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Lys Asn Lys Ile Gln Val Val Val Leu Glu Asn Glu Gly Leu Gln Gln
    50                  55                  60

Gln Leu Lys Ser Gln Arg Gln Glu Glu Thr Leu Arg Glu Gln Thr Leu
65                  70                  75                  80

Leu Asp Ala Ser Gly Asn Met His Asn Ser Trp Ile Thr Thr Gly Glu
                85                  90                  95

Asp Ser Gly Val Gly Glu Thr Ser Lys Arg Pro Phe Ser His Asp Asn
            100                 105                 110

Ala Asp Phe Gly Lys Ala Ala Ser Ala Gly Glu Gln Leu Glu Leu Glu
        115                 120                 125

Lys Leu Lys Leu Thr Tyr Glu Glu Lys Cys Glu Ile Glu Glu Ser Gln
    130                 135                 140

Leu Lys Phe Leu Arg Asn Asp Leu Ala Glu Tyr Gln Arg Thr Cys Glu
145                 150                 155                 160

Asp Leu Lys Glu Gln Leu Lys His Lys Glu Phe Leu Leu Ala Ala Asn
                165                 170                 175

Thr Cys Asn Arg Val Gly Gly Leu Cys Leu Lys Cys Ala Gln His Glu
            180                 185                 190

Ala Val Leu Ser Gln Thr His Thr Asn Val His Met Gln Thr Ile Glu
        195                 200                 205

Arg Leu Val Lys Glu Arg Asp Asp Leu Met Ser Ala Leu Val Ser Val
    210                 215                 220

Arg Ser Ser Leu Ala Asp Thr Gln Gln Arg Glu Ala Ser Ala Tyr Glu
225                 230                 235                 240

Gln Val Lys Gln Val Leu Gln Ile Ser Glu Glu Ala Asn Phe Glu Lys
                245                 250                 255

Thr Lys Ala Leu Ile Gln Cys Asp Gln Leu Arg Lys Glu Leu Glu Arg
            260                 265                 270

Gln Ala Glu Arg Leu Glu Lys Glu Leu Ala Ser Gln Gln Glu Lys Arg
        275                 280                 285

Ala Ile Glu Lys Asp Met Met Lys Lys Glu Ile Thr Lys Glu Arg Glu
    290                 295                 300

Tyr Met Gly Ser Lys Met Leu Ile Leu Ser Gln Asn Ile Ala Gln Leu
305                 310                 315                 320

Glu Ala Gln Val Glu Lys Val Thr Lys Glu Lys Ile Ser Ala Ile Asn
                325                 330                 335

Gln Leu Glu Glu Ile Gln Ser Gln Leu Ala Ser Arg Glu Met Asp Val
```

340 345 350

Thr Lys Val Cys Gly Glu Met Arg Tyr Gln Leu Asn Lys Thr Asn Met
355 360 365

Glu Lys Asp Glu Ala Glu Lys Glu His Arg Glu Phe Arg Ala Lys Thr
370 375 380

Asn Arg Asp Leu Glu Ile Lys Asp Gln Glu Ile Glu Lys Leu Arg Ile
385 390 395 400

Glu Leu Asp Glu Ser Lys Gln His Leu Glu Gln Glu Gln Gln Lys Ala
405 410 415

Ala Leu Ala Arg Glu Glu Cys Leu Arg Leu Thr Glu Leu Leu Gly Glu
420 425 430

Ser Glu His Gln Leu His Leu Thr Arg Gln Glu Lys Asp Ser Ile Gln
435 440 445

Gln Ser Phe Ser Lys Glu Ala Lys Ala Gln Ala Leu Gln Ala Gln Gln
450 455 460

Arg Glu Gln Glu Leu Thr Gln Lys Ile Gln Gln Met Glu Ala Gln His
465 470 475 480

Asp Lys Thr Glu Asn Glu Gln Tyr Leu Leu Leu Thr Ser Gln Asn Thr
485 490 495

Phe Leu Thr Lys Leu Lys Glu Glu Cys Cys Thr Leu Ala Lys Lys Leu
500 505 510

Glu Gln Ile Ser Gln Lys Thr Arg Ser Glu Ile Ala Gln Leu Ser Gln
515 520 525

Glu Lys Arg Tyr Thr Tyr Asp Lys Leu Gly Lys Leu Gln Arg Arg Asn
530 535 540

Glu Glu Leu Glu Glu Gln Cys Val Gln His Gly Arg Val His Glu Thr
545 550 555 560

Met Lys Gln Arg Leu Arg Gln Leu Asp Lys His Ser Gln Ala Thr Ala
565 570 575

Gln Gln Leu Val Gln Leu Leu Ser Lys Gln Asn Gln Leu Leu Leu Glu
580 585 590

Arg Gln Ser Leu Ser Glu Glu Val Asp Arg Leu Arg Thr Gln Leu Pro
595 600 605

Ser Met Pro Gln Ser Asp Cys
610 615

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 313 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

GCGACCTCTT CTGCGGCCGG CCTGGGCAGG TGTCTTCCTC GAGAGGCAGG CAGGGGATCC 60

CGGACACTAG CTTTATCGTC ATCTGGGAAA TTGTTAAAAA TGCAAATTCG CAAGTTTGAG 120

AGCCATGGTT CCAAGAAACT GCATAAGCAT ACGAAATAAG TTGCAGCCTC CCGACTTATA 180

CCCTGGTACT TCTAGTCTAA AACAGGATTT GACTCTACTA ATCCAGCCTT ATACAGGATG 240

CTGTGTTCTT TGCTCCTTTG TGAATGTCTG TTGCTGGTAG CTGGTTATGC TCATGATGAT 300

GACTGGATTG ACC 313

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 677 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CCTTGGATGA TGCATTAAGT GATATTTTAA TTAATTTTAA GTTTCATGAT TTTGAAACAT 60

GGAAGTGGCG ATTCGAAGAT TCCTTTGGAG TGGATCCATA TAATGTGTTA ATGGTAATTC 120

TTTGTCTGCT CTGCATCGTG GTTTTAGTGG CTACTGAGCT GTGGACATAT GTATGTTGGT 180

ACACTCAGTT GAGACGTGTT TTAATCATCA GCTTTCTGTT CAGTTTGGGA TGGAATTGGA 240

TGTATTTATA TAAGCTAGCT TTTGCACAGC ATCAGGCTGA AGTCGCCAAG ATGGAGCCAT 300

TAAACAATGT GTGTGCCAAA AAGATGGACT GGACTGGAAG TATCTGGGAA TGGTTTAGAA 360

GTTCATGGAC CTATAAGGAT GACCCATGCC AAAAATACTA TGAGCTCTTA CTAGTCAACC 420

CTATTTGGTT GGTCCCACCA ACAAAGGCAC TTGCAGTTAC ATTCACCACA TTTGTAACGG 480

AGCCATTGAA GCATATTGGA AAAGGAACTG GGGAATTTAT TAAAGCACTC ATGAAGGAAA 540

TTCCAGCGCT GCTTCATCTT CCAGTGCTGA TAATTATGGC ATTAGCCATC CTGAGTTTCT 600

GCTATGGTGC TGGAAAATCA GTTCATGTGC TGAGACATAT AGGCGGTCCT GAGAGCGAAC 660

CTCCCCAGGC ACTTCGG 677

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 189 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

Met Val Ile Leu Cys Leu Leu Cys Ile Val Val Leu Val Ala Thr Glu
1 5 10 15

Leu Trp Thr Tyr Val Cys Trp Tyr Thr Gln Leu Arg Arg Val Leu Ile
20 25 30

Ile Ser Phe Leu Phe Ser Leu Gly Trp Asn Trp Met Tyr Leu Tyr Lys
35 40 45

Leu Ala Phe Ala Gln His Gln Ala Glu Val Ala Lys Met Glu Pro Leu
50 55 60

Asn Asn Val Cys Ala Lys Lys Met Asp Trp Thr Gly Ser Ile Trp Glu
65 70 75 80

Trp Phe Arg Ser Ser Trp Thr Tyr Lys Asp Asp Pro Cys Gln Lys Tyr
85 90 95

Tyr Glu Leu Leu Leu Val Asn Pro Ile Trp Leu Val Pro Pro Thr Lys
100 105 110

Ala Leu Ala Val Thr Phe Thr Thr Phe Val Thr Glu Pro Leu Lys His
115 120 125

Ile Gly Lys Gly Thr Gly Glu Phe Ile Lys Ala Leu Met Lys Glu Ile
130 135 140

Pro Ala Leu Leu His Leu Pro Val Leu Ile Ile Met Ala Leu Ala Ile
145 150 155 160

Leu Ser Phe Cys Tyr Gly Ala Gly Lys Ser Val His Val Leu Arg His
165 170 175

Ile Gly Gly Pro Glu Ser Glu Pro Pro Gln Ala Leu Arg
180 185

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 470 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

AGACGGCAGG AGGAATTGAT TATAGACCTG ATGGTGGAGC AGGTGATGCC GATTTCCATT 60

ATAGGGGCCA AATGGGCCCC ATTGAGCAAG GCCCTTATGC CAAAATGTAT GAGGGTAGAA 120

GAGAGATTTT GAGAGAGAGA GATGTTGACT TGAGATTTCA GGCTGGTCTC GAACTCCTGA 180

CCTCAAGTGA CCCGCCCTTG TCGGCCTCCC AAAGTGCTGG GATTACAGGC ATGAGCCATT 240

GTGCCCAGCC TATATAGTGT GAAGCTTTTA GGAAAATCAG AACAGGGTAG ACAGTTGTTA 300

AAAACAATGT TTAAATGGAA TAATGTTGAA TGTTTACAGG CTGTAAGAAT TATTGTATAC 360

ACAAAATAAT ACACAAAGTT TGTACTTTGT GTACAAATAC AAATTTGTAC TTTGTGTACA 420

AATAATACAA AAAGTTTGTA TACACAAAAA AAAAAAAAAA AAAAAAAAAA 470

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 2702 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CTGGAGTCCA CGCGGATTTT CGAAGCTGGG GCTGGCAAGA GGCCGCTGGA CACCACGCTC 60

CAGTCGTCAG CCCACTTCCT AGCTGAACAG CGCGAGGCGG CGGCAGCGAG CCGGGTCCCA 120

CCATGGCCGC GAATTATTCC AGTACCAGTA CCCGGAGAGA ACATGTCAAA GTTAAAACCA 180

GCTCCCAGCC AGGCTTCCTG GAACGGCTGA GCGAGACCTC GGGTGGGATG TTTGTGGGGC 240

TCATGGCCTT CCTGCTCTCC TTCTACCTAA TTTTCACCAA TGAGGGCCGC GCATTGAAGA 300

CGGCAACCTC ATTGGCTGAG GGGCTCTCGC TTGTGGTGTC TCCTGACAGC ATCCACAGTG 360

TGGCTCCGGA GAATGAAGGA AGGCTGGTGC ACATCATTGG CGCCTTACGG ACATCCAAGC 420

TTTTGTCTGA TCCAAACTAT GGGGTCCATC TTCCGGCTGT GAAACTGCGG AGGCACGTGG 480

AGATGTACCA ATGGGTAGAA ACTGAGGAGT CCAGGGAGTA CACCGAGGAT GGGCAGGTGA 540

AGAAGGAGAC GAGGTATTCC TACAACACTG AATGGAGGTC AGAAATCATC AACAGCAAAA 600

ACTTCGACCG AGAGATTGGC CACAAAAACC CCAGCTTCCT CTCTCCCACA GTGCCATGGC 660

AGTGGAGTCA TTCATGGCAA CAGCCCCCTT TGTCCAAATT GGCAGGTTTT TCCTCTCGTC 720

AGGCCTCATC GACAAAGTCG ACAACTTCAA GTCCCTGAGC CTATCCAAGC TGGAGGACCC 780

TCATGTGGAC ATCATTCGCC GTGGAGACTT TTTCTACCAC AGCGAAAATC CCAAGTATCC 840

AGAGGTGGGA GACTTGCGTG TCTCCTTTTC CTATGCTGGA CTGAGCGGCG ATGACCCTGA 900

CCTGGGCCCA GCTCACGTGG TAACCTGGCT TCCCAGGGGC AGACACTAAG TCAGAGCCTC 960

ACGACTTTCC TGGACACAGA CACCTTGGTC AATGTCAGGA GCGCTTGGAC CCCCTTTTCC 1020

CTGGGGAAAG GCACACTCTC GCACACACTC TCAGCCAGGC ACGCTTCTGA GCAGTTTCAG 1080

AGCTCCCATG TCCCCACAGC CATCCATGGA CCCCACGTTA AGAAGGGCAG CTCAAAAGGG 1140

GTCTCATAGT CGCACCTTAT GACAGGTGTT CCAGTCACAC ACAGACCCTC TCCCCAAGCC 1200

CGTTTTGATC TGTCAATAAT TGGTCTTGCG TTCCTGGCCT ATGTGCAGTC CTGCCCCATC 1260

CCCTGCTCTG CGCACTGCCC AAGAGCTTTG AATGCCTGGA GCTTTGAATG GAGCAGCTCA 1320

GCCAGAGCTG CAGAGGTGGA TGCATCCCAG ATGGATGTAT AGAGAGAGAA GCCCCAGGGT 1380

CTCTGTGCTC ACTTCCCCAG CCGGCACCCA GTCCCGGGAG GGTGGGCCAT GGCTCTCATG 1440

GGCGTGTCTC CCGCTGGTCA CCCCTCAGCT CTAACACCAG GTCCTCTGAC CAGGTCACTG 1500

TGATTGCCCG GCAGCGGGGT GACCAGCTAG TCCCATTCTC CACCAAGTCT GGGGATACCT 1560

TACTGCTCCT GCACCACGGG GACTTCTCAG CAGAGGAGGT GTTTCATAGA GAACTAAGGA 1620

GCAACTCCAT GAAGACCTGG GGCCTGCGGG CAGCTGGCTG GATGGCCATG TTCATGGGCC 1680

TCAACCTTAT GACACGGATC CTCTACACCT TGGTGGACTG GTTTCCTGTT TTCCGAGACC 1740

TGGTCAACAT TGGCCTGAAA GCCTTTGCCT TCTGTGTGGC CACCTCGCTG ACCCTGCTGA 1800

CCGTGGCGGC TGGCTGGCTC TTCTACCGAC CCCTGTGGGC CCTCCTCATT GCCGGCCTGG 1860

CCCTTGTGCC CATCCTTGTT GCTCGGACAC GGGTGCCAGC CAAAAAGTTG GAGTGAAAAG 1920

ACCCTGGCAC CCGCCCGACA CCTGCGTGAG CCCTAGGATC CAGGTCCTCT CTCACCTCTG 1980

ACCCAGCTCC ATGCCAGAGC AGGAGCCCCG GTCAATTTTG GACTCTGCAC CCCCTCTCCT 2040

CTTCAGGGGC CAGACTTGGC AGCATGTGCA CCAGGTTGGT GTTCACCAGC TCATGTCTTC 2100

CCCACATCTC TTCTTGCCAG TAAGCAGCTT TGGTGGGCAG CAGCAGCTCA TGAATGGCAA 2160

GCTGACAGCT TCTCCTGCTG TTTCCTTCCT CTCTTGGACT GAGTGGGTAC GGCCAGCCAC 2220

TCAGCCCATT GGCAGCTGAC AACGCAGACA CGCTCTACGG AGGCCTGCTG ATAAAGGGCT 2280

CAGCCTTGCC GTGTGCTGCT TCTCATCACT GCACACAAGT GCCATGCTTT GCCACCACCA 2340

CCAAGCACAT CTGTGATCCT GAAGGGCGGC CGTTAGTCAT TACTGCTGAG TCCTGGGTCA 2400

CCAGCAGACA CACTGGGCAT GGACCCCTCA AAGCAGGCAC ACCCAAAACA CAAGTCTGTG 2460

GCTAGAACCT GATGTGGTGT TTAAAAGAGA AGAAACACTG AAGATGTCCT GAGGAGAAAA 2520

GCTGGACATA TACTGGGCTT CACACTTATC TTATGGCTTG GCAGAATCTT TGTAGTGTGT 2580

GGGATCTCTG AAGGCCCTAT TTAAGTTTTT CTTCGTTACT TTGCTGCTTC ATGTGTACTT 2640

TCCTACCCCA AGAGGAAGTT TTCTGAAATA AGATTTAAAA ACAAAACAAA AAAAAAAAAA 2700

AA 2702

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 211 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

Met Ala Ala Asn Tyr Ser Ser Thr Ser Thr Arg Arg Glu His Val Lys
1 5 10 15

Val Lys Thr Ser Ser Gln Pro Gly Phe Leu Glu Arg Leu Ser Glu Thr
20 25 30

Ser Gly Gly Met Phe Val Gly Leu Met Ala Phe Leu Leu Ser Phe Tyr
35 40 45

Leu Ile Phe Thr Asn Glu Gly Arg Ala Leu Lys Thr Ala Thr Ser Leu

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    50                  55                  60

Ala Glu Gly Leu Ser Leu Val Val Ser Pro Asp Ser Ile His Ser Val
65                  70                  75                  80

Ala Pro Glu Asn Glu Gly Arg Leu Val His Ile Ile Gly Ala Leu Arg
                85                  90                  95

Thr Ser Lys Leu Leu Ser Asp Pro Asn Tyr Gly Val His Leu Pro Ala
            100                 105                 110

Val Lys Leu Arg Arg His Val Glu Met Tyr Gln Trp Val Glu Thr Glu
        115                 120                 125

Glu Ser Arg Glu Tyr Thr Glu Asp Gly Gln Val Lys Lys Glu Thr Arg
    130                 135                 140

Tyr Ser Tyr Asn Thr Glu Trp Arg Ser Glu Ile Ile Asn Ser Lys Asn
145                 150                 155                 160

Phe Asp Arg Glu Ile Gly His Lys Asn Pro Ser Phe Leu Ser Pro Thr
                165                 170                 175

Val Pro Trp Gln Trp Ser His Ser Trp Gln Gln Pro Pro Leu Ser Lys
            180                 185                 190

Leu Ala Gly Phe Ser Ser Arg Gln Ala Ser Ser Thr Lys Ser Thr Thr
        195                 200                 205

Ser Ser Pro
    210
```

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3395 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

```
ATCTTCCTGC CCTTCACCTG CATTGGCTAC ACGGCCACCA ATCAGGACTT CATCCAGCGC      60

CTGAGCACAC TGATCCGGCA GGCCATCGAG CGGCAGCTGC CTGCCTGGAT CGAGGCTGCC     120

AACCAGCGGG AGGAGGGCCA GGGTGAACAG GGCGAGGAGG AGGATGAGGA GGAGGAAGAA     180

GAGGAGGACG TGGCTGAGAA CCGCTACTTT GAAATGGGGC CCCCAGACGT GGAGGAGGAG     240
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GAGGGAGGAG GCCAGGGGGA GGAAGAGGAG GAGGAAGAGG ARGATGAAGA RGCCGAGGAG 300

GAGCGCCTGG CTCTGGAATG GGCCCTGGGC GCGGACGAAG ACTTCCTGCT GGAGCACATC 360

CGCATCCTCA AGGTGCTGTG GTGCTTCCTG ATCCATGTGC AGGGCAGTAT CCGCCAGTTC 420

GCCGCCTGCC TTGTGCTCAC CGACTTCGGC ATCGCAGTCT TCGAGATCCC GCACCAGGAG 480

TCTCGGGGCA GCAGCCAGCA CATCCTCTCC TCCCTGCGCT TTGTCTTTTG CTTCCCGCAT 540

GGCGACCTCA CCGAGTTTGG CTTCCTCATG CCGGAGCTGT GTCTGGTGCT CAAGGTACGG 600

CACAGTGAGA ACACGCTCTT CATTATCTCG GACGCCGCCA ACCTGCACGA GTTCCACGCG 660

GACCTGCGCT CATGCTTTGC ACCCCAGCAC ATGGCCATGC TGTGTAGCCC CATCCTCTAC 720

GGCAGCCACA CCAGCCTGCA GGAGTTCCTG CGCCAGCTGC TCACCTTCTA CAAGGTGGCT 780

GGCGGCTGCC AGGAGCGCAG CCAGGGCTGC TTCCCCGTCT ACCTGGTCTA CAGTGACAAG 840

CGCATGGTGC AGACGGCCGC CGGGGACTAC TCAGGCAACA TCGAGTGGGC CAGCTGCACA 900

CTCTGTTCAG CCGTGCGGCG CTCCTGCTGC GCGCCCTCTG AGGCCGTCAA GTCCGCCGCC 960

ATCCCCTACT GGCTGTTGCT CACGCCCCAG CACCTCAACG TCATCAAGGC CGACTTCAAC 1020

CCCATGCCCA ACCGTGGCAC CCACAACTGT CGCAACCGCA ACAGCTTCAA GCTCAGCCGT 1080

GTGCCGCTCT CCACCGTGCT GCTGGACCCC ACACGCAGCT GTACCCAGCC TCGGGGCGCC 1140

TTTGCTGATG GCCACGTGCT AGAGCTGCTC GTGGGGTACC GCTTTGTCAC TGCCATCTTC 1200

GTGCTGCCCC ACGAGAAGTT CCACTTCCTG CGCGTCTACA ACCAGCTGCG GGCCTCGCTG 1260

CAGGACCTGA AGACTGTGGT CATCGCCAAG ACCCCCGGGA CGGGAGGCAG CCCCCAGGGC 1320

TCCTTTGCGG ATGGCCAGCC TGCCGAGCGC AGGGCCAGCA ATGACCAGCG TCCCCAGGAG 1380

GTCCCAGCAG AGGCTCTGGC CCCGGCCCCA GTGGAAGTCC CAGCTCCAGC CCCTGCAGCA 1440

GCCTCAGCCT CAGGCCCAGC GAAGACTCCG GCCCCAGCAG AGGCCTCAAC TTCAGCTTTG 1500

GTCCCAGAGG AGACGCCAGT GGAAGCTCCA GCCCCACCCC CAGCCGAGGC CCCTGCCCAG 1560

TACCCGAGTG AGCACCTCAT CCAGGCCACC TCGGAGGAGA ATCAGATCCC CTCGCACTTG 1620

CCTGCCTGCC CGTCGCTCCG GCACGTCGCC AGCCTGCGGG GCAGCGCCAT CATCGAGCTC 1680

TTCCACAGCA GCATTGCTGA GGTTGAAAAC GAGGAGCTGA GGCACCTCAT GTGGTCCTCG 1740

GTGGTGTTCT ACCAGACCCC AGGGCTGGAG GTGACTGCCT GCGTGCTGCT CTCCACCAAG 1800

GCTGTGTACT TTGTGCTCCA CGACGGCCTC CGCCGCTACT TCTCAGAGCC ACTGCAGGAT 1860

TTCTGGMATC AGAAAAACAC SGACTACAAC AACAGCCCTT TCCACATCTC CCAGTGCTTC 1920

GTGCTAAAGC TTAGTGACCT GCAGTCAGTC AATGTGGGGC TTTTCGACCA GCATTTCCGG 1980

CTGACGGGTT CCACCCCGAT GCAGGTGGTM ACGTGCTTGA CGCGGGACAG CTACCTGACG 2040

CACTGCTTCC TCCAGCACCT CATGGTCGTG CTGTCCTCTC TGGAACGCAC GCCCTCGCCG 2100

GAGCCTGTTG ACAAGGACTT CTACTCCGAG TTTGGGAACA AGACCACAGG GAAGATGGAG 2160

AACTACGAGC TGATCCACTC TAGTCGCGTC AAGTTTACCT ACCCCAGTGA GGAGGAGATT 2220

GGGGACCTGA CGTTCACTGT GGCCCAAAAG ATGGCTGAGC CAGAGAAGGC CCCAGCCCTC 2280

AGCATCCTGC TGTACGTGCA GGCCTTCCAG GTGGGCATGC CACCCCCTGG GTGCTGCAGG 2340

GGCCCCCTGC GCCCCAAGAC ACTCCTGCTC ACCAGCTCCG AGATCTTCCT CCTGGATGAG 2400

GACTGTGTCC ACTACCCACT GCCCGAGTTT GCCAAAGAGC CGCCGCAGAG AGACAGGTAC 2460

CGGCTGGACG ATGGCCGCCG CGTCCGGGAC CTGGACCGAG TGCTCATGGG CTACCAGACC 2520

TACCCGCAGG CCCTCACCCT CGTCTTCGAT GACGTGCAAG GTCATGACCT CATGGGCAGT 2580

GTCACCCTGG ACCACTTTGG GGAGGTGCCA GGTGGCCCGG CTAGAGCCAG CCAGGGCCGT 2640

GAAGTCCAGT GGCAGGTGTT TGTCCCCAGT GCTGAGAGCA GAGAGAAGCT CATCTCGCTG 2700

TTGGCTCGCC AGTGGGAGGC CCTGTGTGGC CGTGAGCTGC CTGTCGAGCT CACCGGCTAG 2760

CCCAGGCCAC AGCCAGCCTG TCGTGTCCAG CCTGACGCCT ACTGGGGCAG GGCAGCAGGC 2820

TTTTGTGTTC TCTAAAAATG TTTTATCCTC CCTTTGGTAC CTTAATTTGA CTGTCCTCGC 2880

AGAGAATGTG AACATGTGTG TGTGTTGTGT TAATTCTTTC TCATGTTGGG AGTGAGAATG 2940

CCGGGCCCCT CAGGGCTGTC GGTGTGCTGT CAGCCTCCCA CAGGTGGTAC AGCCGTGCAC 3000

ACCAGTGTCG TGTCTGCTGT TGTGGGACCG TTGTTAACAC GTGACACTGT GGGTCTGACT 3060

TTCTCTTCTA CACGTCCTTT CCTGAAGTGT CGAGTCCAGT CCTTTGTTGC TGTTGCTGTT 3120

GCTGTTGCTG TTGCTGTTGG CATCTTGCTG CTAATCCTGA GGCTGGTAGC AGAATGCACA 3180

TTGGAAGCTC CCACCCCATA TTGTTCTTCA AAGTGGAGGT CTCCCCTGAT CCAGACAAGT 3240

GGGAGAGCCC GTGGGGGCAG GGGACCTGGA GCTGCCAGCA CCAAGCGTGA TTCCTGCTGC 3300

CTGTATTCTC TATTCCAATA AAGCAGAGTT TGACACCGTC AAAAAAAAAA AAAAAAAAAA 3360

AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAA 3395

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 848 amino acids
(B) TYPE: amino acid

(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

```
Met Gly Pro Pro Asp Val Glu Glu Glu Glu Gly Gly Gly Gln Gly Glu
1               5                  10                  15

Glu Glu Glu Glu Glu Glu Glu Asp Glu Glu Ala Glu Glu Glu Arg Leu
            20                  25                  30

Ala Leu Glu Trp Ala Leu Gly Ala Asp Glu Asp Phe Leu Leu Glu His
        35                  40                  45

Ile Arg Ile Leu Lys Val Leu Trp Cys Phe Leu Ile His Val Gln Gly
    50                  55                  60

Ser Ile Arg Gln Phe Ala Ala Cys Leu Val Leu Thr Asp Phe Gly Ile
65                  70                  75                  80

Ala Val Phe Glu Ile Pro His Gln Glu Ser Arg Gly Ser Ser Gln His
                85                  90                  95

Ile Leu Ser Ser Leu Arg Phe Val Phe Cys Phe Pro His Gly Asp Leu
            100                 105                 110

Thr Glu Phe Gly Phe Leu Met Pro Glu Leu Cys Leu Val Leu Lys Val
        115                 120                 125

Arg His Ser Glu Asn Thr Leu Phe Ile Ile Ser Asp Ala Ala Asn Leu
    130                 135                 140

His Glu Phe His Ala Asp Leu Arg Ser Cys Phe Ala Pro Gln His Met
145                 150                 155                 160

Ala Met Leu Cys Ser Pro Ile Leu Tyr Gly Ser His Thr Ser Leu Gln
                165                 170                 175

Glu Phe Leu Arg Gln Leu Leu Thr Phe Tyr Lys Val Ala Gly Gly Cys
            180                 185                 190

Gln Glu Arg Ser Gln Gly Cys Phe Pro Val Tyr Leu Val Tyr Ser Asp
        195                 200                 205

Lys Arg Met Val Gln Thr Ala Ala Gly Asp Tyr Ser Gly Asn Ile Glu
    210                 215                 220

Trp Ala Ser Cys Thr Leu Cys Ser Ala Val Arg Arg Ser Cys Cys Ala
225                 230                 235                 240
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Pro Ser Glu Ala Val Lys Ser Ala Ala Ile Pro Tyr Trp Leu Leu Leu
                245                 250                 255

Thr Pro Gln His Leu Asn Val Ile Lys Ala Asp Phe Asn Pro Met Pro
            260                 265                 270

Asn Arg Gly Thr His Asn Cys Arg Asn Arg Asn Ser Phe Lys Leu Ser
        275                 280                 285

Arg Val Pro Leu Ser Thr Val Leu Leu Asp Pro Thr Arg Ser Cys Thr
    290                 295                 300

Gln Pro Arg Gly Ala Phe Ala Asp Gly His Val Leu Glu Leu Leu Val
305                 310                 315                 320

Gly Tyr Arg Phe Val Thr Ala Ile Phe Val Leu Pro His Glu Lys Phe
                325                 330                 335

His Phe Leu Arg Val Tyr Asn Gln Leu Arg Ala Ser Leu Gln Asp Leu
            340                 345                 350

Lys Thr Val Val Ile Ala Lys Thr Pro Gly Thr Gly Gly Ser Pro Gln
        355                 360                 365

Gly Ser Phe Ala Asp Gly Gln Pro Ala Glu Arg Arg Ala Ser Asn Asp
    370                 375                 380

Gln Arg Pro Gln Glu Val Pro Ala Glu Ala Leu Ala Pro Ala Pro Val
385                 390                 395                 400

Glu Val Pro Ala Pro Ala Pro Ala Ala Ala Ser Ala Ser Gly Pro Ala
                405                 410                 415

Lys Thr Pro Ala Pro Ala Glu Ala Ser Thr Ser Ala Leu Val Pro Glu
            420                 425                 430

Glu Thr Pro Val Glu Ala Pro Ala Pro Pro Pro Ala Glu Ala Pro Ala
        435                 440                 445

Gln Tyr Pro Ser Glu His Leu Ile Gln Ala Thr Ser Glu Glu Asn Gln
    450                 455                 460

Ile Pro Ser His Leu Pro Ala Cys Pro Ser Leu Arg His Val Ala Ser
465                 470                 475                 480

Leu Arg Gly Ser Ala Ile Ile Glu Leu Phe His Ser Ser Ile Ala Glu
                485                 490                 495

Val Glu Asn Glu Glu Leu Arg His Leu Met Trp Ser Ser Val Val Phe
            500                 505                 510

Tyr Gln Thr Pro Gly Leu Glu Val Thr Ala Cys Val Leu Leu Ser Thr
        515                 520                 525

Lys Ala Val Tyr Phe Val Leu His Asp Gly Leu Arg Arg Tyr Phe Ser
```

530 535 540

Glu Pro Leu Gln Asp Phe Trp Xaa Gln Lys Asn Thr Asp Tyr Asn Asn
545 550 555 560

Ser Pro Phe His Ile Ser Gln Cys Phe Val Leu Lys Leu Ser Asp Leu
565 570 575

Gln Ser Val Asn Val Gly Leu Phe Asp Gln His Phe Arg Leu Thr Gly
580 585 590

Ser Thr Pro Met Gln Val Val Thr Cys Leu Thr Arg Asp Ser Tyr Leu
595 600 605

Thr His Cys Phe Leu Gln His Leu Met Val Val Leu Ser Ser Leu Glu
610 615 620

Arg Thr Pro Ser Pro Glu Pro Val Asp Lys Asp Phe Tyr Ser Glu Phe
625 630 635 640

Gly Asn Lys Thr Thr Gly Lys Met Glu Asn Tyr Glu Leu Ile His Ser
645 650 655

Ser Arg Val Lys Phe Thr Tyr Pro Ser Glu Glu Glu Ile Gly Asp Leu
660 665 670

Thr Phe Thr Val Ala Gln Lys Met Ala Glu Pro Glu Lys Ala Pro Ala
675 680 685

Leu Ser Ile Leu Leu Tyr Val Gln Ala Phe Gln Val Gly Met Pro Pro
690 695 700

Pro Gly Cys Cys Arg Gly Pro Leu Arg Pro Lys Thr Leu Leu Leu Thr
705 710 715 720

Ser Ser Glu Ile Phe Leu Leu Asp Glu Asp Cys Val His Tyr Pro Leu
725 730 735

Pro Glu Phe Ala Lys Glu Pro Pro Gln Arg Asp Arg Tyr Arg Leu Asp
740 745 750

Asp Gly Arg Arg Val Arg Asp Leu Asp Arg Val Leu Met Gly Tyr Gln
755 760 765

Thr Tyr Pro Gln Ala Leu Thr Leu Val Phe Asp Asp Val Gln Gly His
770 775 780

Asp Leu Met Gly Ser Val Thr Leu Asp His Phe Gly Glu Val Pro Gly
785 790 795 800

Gly Pro Ala Arg Ala Ser Gln Gly Arg Glu Val Gln Trp Gln Val Phe
805 810 815

Val Pro Ser Ala Glu Ser Arg Glu Lys Leu Ile Ser Leu Leu Ala Arg
820 825 830

Gln Trp Glu Ala Leu Cys Gly Arg Glu Leu Pro Val Glu Leu Thr Gly
835 840 845

(2) INFORMATION FOR SEQ ID NO:17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1147 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

GGAAGGAGTT CTGGAATTGG AAAACCATCA TTTTTCAACC ATCACAGTAA ATATGGCTCA 60

GGCAAGAATT ATCAATCAAT GCTAAAGCTA GGGGGAAATT TCGCTTAGGA GCAGGATATT 120

AGGGTATTAG TCTGGGCTTA AAGTATCTCC TCACAGATTG TTGTTAGTTT CTGGGGAAAG 180

AATAGTAACC ATGCAATGGA AAAAAATGGA CAACCTCTTG ACTAGGTTAT CAAAATTAAC 240

CTCACCAATA AAGGGTGGAT GTTCAACATG TGCCTTCAAA TGTGACCCAC TGAGAAGGAA 300

ACAACATCAC TGTAACAACA ACAACCAGAA ACGACAGGGG GTTTTGACTG AATTCTTCAA 360

AAATGTCAAT GTCATAGAAG ACAAAGAAAG GTTGTGGAAA TGTTTCAGAT TAAATGATAG 420

TAAAAACACC TGACAACTAA ACATAGTAAG TAATACTAGA CTGGATTCTG TACCAGAGGT 480

AACATAAGTG CTCCAAAGGA CAATGTTAGG TCAACTGGCA AATTGGAATA TAGACAGTCA 540

ATCAGATAAG AAGTATACTT TGATTAAGTA AAAAAAATCC CTATTCTTGG AAAATACACA 600

ATAAAGTATT TTGAGGTAAA GGGCCATAAT GTATGCAATC TACTCTCAAA AAATTCAGAA 660

ACATATATTT GTGTGCATTT GCATGTGCAA CAGTACACAC AAACATACAT AAAGAGAGCA 720

ATTGATAAGG CAAATAAGGT AACATTTAAC AATAATCTGA TACACATAAA TAGAGAAAGA 780

GCAATTGATA AAGTAAATGA GGTAAAATTT AACAATAATC TGAGCAAAAG GTATATGTGT 840

TTTCTTTGAG ACAGTCTGAT TCTTGCAACT TATTCTGTAA GTTGGAACTT ATTTCCAAAC 900

ATGATTGAAA AAAAACCCCG CACTTGGCAA CTTCTTCTCT TTTTCAGCCT AGAAATGTCT 960

GTGTTAAGTG GTTTTTTATT TATTGTTGTT GTTTGTTGTT ATTGTTGTTT TGTTGCCAGG 1020

CTCCAACTCA CAAAATACGA GTTTAAAAAC TGCGTTGTTA TTTTTAGAGA TTTGTGATAA 1080

TACAACTTGT TATAAAATTT ATTCCTCAAT AAATATAATT TCTCTACTAT GCAAAAAAAA 1140

AAAAAAA 1147

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 58 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

Met Ile Glu Lys Lys Pro Arg Thr Trp Gln Leu Leu Leu Phe Phe Ser
1 5 10 15

Leu Glu Met Ser Val Leu Ser Gly Phe Leu Phe Ile Val Val Val Cys
20 25 30

Cys Tyr Cys Cys Phe Val Ala Arg Leu Gln Leu Thr Lys Tyr Glu Phe
35 40 45

Lys Asn Cys Val Val Ile Phe Arg Asp Leu
50 55

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1013 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

CCTTTTTAAA AAATATCTGA AAAAAGCTTC ATATCTTTAC AAACTCATAA AATAGCTGAT 60

TGGGCCATGG AGGAGATGAG GCTGTTTAGA ACTGGTTTTG TTTCAAGTTT GTCAATTTTC 120

CCTGTATGAG AACTTGGGTA AAGCACAAAG AAACATACAG TGCTAGTAAC AGGTCTCCTG 180

CGCCCTGGAA CTAAGTGTTT GGAGGAAGGA CTAAACCCCG GGGGAGGTGA GTATAAAATA 240

ATTCCACTAA GATCACCTCC TCAGTCCCCA GAAGGCTGAT GGTGGATCCT CTGGCCATCT 300

CCTGTGGGGT CTTACTGCTC CTCTGCCATT TCTCTATGCC TGAAGACACG AAGATGATAT 360

CAAGGCAGAG CTACCATATC GCAGCCAGTC TCTAGGCTAC TGCTGTGCAG TGGCTCCCAC 420

TTTCTAATGC TTTTTTGTTT TTGCTTTTTC TAACAAAACA ATCTTTTTTC AAAATGAATT 480

CCAACCCCTG CTAGTTCCTT CGCTGCCTCC ATACTGTTTT AGGCAGCACC GTTTATGTGA 540

CAGAGTCCGT GTTTCTCAAA TGCATGGTGT TCCTCAGGTG GAGAGTGGGC AGAAGTTTTT 600

GCAACACTTT TTTTTTAAGT TATTGGGTGC AAAATCCCAA ACCAGGATAT GTGTATGTCT 660

GTGTGTTTAT GTTTTTTATT TGACCCTCCC CTCTTTCAAC CTACCCCCTT TTATATCTAA 720

TGTAGAAAAA GCGAAATTGA ATCTGGAAAG CAAACTGTTG TATATAGTTG CGGTAACAAT 780

CATGAAGAGA GAGCCGGGCT GTCCCCTCAG TAATTCATTT TAAATAACAA ATTATTTAAA 840

AATAAAATTC ATGCCAGAGC CAGCTGAAGA GGCCTTCCTT CATCACCACT GAGGCCACCC 900

CCAATCTGGG CCCTCTGTCC ATCTGGCATG TCTCCTCCCA GCAAGATTCA TCTGTTCAAT 960

GCCATTTGCG TTTCAATAAA GTTATCTCCT GTACTGTCAA AAAAAAAAAA AAA 1013

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 87 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

Met His Gly Val Pro Gln Val Glu Ser Gly Gln Lys Phe Leu Gln His
1 5 10 15

Phe Phe Phe Lys Leu Leu Gly Ala Lys Ser Gln Thr Arg Ile Cys Val
20 25 30

Cys Leu Cys Val Tyr Val Phe Tyr Leu Thr Leu Pro Ser Phe Asn Leu
35 40 45

Pro Pro Phe Ile Ser Asn Val Glu Lys Ala Lys Leu Asn Leu Glu Ser
50 55 60

Lys Leu Leu Tyr Ile Val Ala Val Thr Ile Met Lys Arg Glu Pro Gly
65 70 75 80

Cys Pro Leu Ser Asn Ser Phe

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 1763 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

TCGGGATAAA AAGCAAGAAA AGAAAGAGAA GACTGAGAAT AAGAAGATCT CTTTGAAAAT 60

AAAATAAGAC TGCTAAAAGT ATTTGGTATA CAGTCTGGAA AATAAAGTTG AGGGAATCTC 120

TCCAGATAAA GAGCAAAAAG AAATAGATAG AAAAATATAA AGAAAGAAAA AAGACATAGA 180

CAATCAATAT GTAATGTTAG GAGTTCCTGG AAGAGAGAAC AGAGACAGTG TAGGTGAAGA 240

AATAAAAAGA AAAAGAATTG AAGAACAGAG CAAGCTAAGT CTCCAGATTG AGAGGGCCCA 300

ATACAATCTA CATCTAGACA CAATATTGTA AAATTTTGGA ATATTAAGGA TAGAAGGAAG 360

ATATTAAAGT GGCCAGGGAG AAAACAAATG AGGTCATCAC GATTAGCTCA ACACAAAAAT 420

GGATGAGAAA TAGACTGCTA ACAGATTTGT CATCAGCAAC ACTGAATGCC AGAAGTCAAT 480

GGATCAACAT CTTCAGAGCT TAAGGAAAAT TTTTGTACCT AGAATTTCAT AGTAAGGCAG 540

ACTGTCAAGA AGAACATCAA AGTGAAGACA TTTTCTGTCA GGCAAATTTT CAGAAAGTCT 600

CCTTTGCACC CTTACTGAGG AAGTATCTTG AGGAAATTCT CCAGCAAAAT GAGGATGAAA 660

ACCAGGAAAG AAGAAGAAAT GGGATCCATA AAACAGTGGA CCTTACTTAG GATGTCTCAT 720

TCTAGAGTGA CAGCCAAAAG GGTATCTCAC CCTAGAGTGA CAGCTATCCA GCAGACTAAT 780

TTCAGATGAG AGCATACTGT CTCGGGCTTT CTGGGAAGAA TGTGCATTCA GTGCCATAGA 840

TAGTATCACT GAAGAGCTGG GATGCTTGAG AAGATTATTT AGTCAAGAAA AAAGAAAGAC 900

AAATCAACAA TATGTCAAAA AATTCAGGTC CAATTATAGA GCAAAATAAA ATGAGGCATG 960

ATTTTGAGTT ATTCATGAAG AATAAGAAGA GGCTTGATAG GTACATTTCC TTTTCTATGG 1020

CACAGGCATG ATGATATTGG GTGTGTAGGG AAGAAAATAT CCTAGCTTAT ACTAGGCTCC 1080

CAGTAAGAAG TATTTAAATA GCCAAAATAA TGTGGATATC ATTTATTAGT ATTCAATGTT 1140

CAGATCAGCC TATTAACAAA GTGTGAAAGG TTTCATTTTT TATTCAGAAC TGAAGTTGAA 1200

AGTAATTAAT GCTGACAAAG GGAAAGAAAG CAGAAAGAGA TTGAGAATTA GAGGAAGAGA 1260

AGTGGAATCA AAGGTAGAGA TACTTATATA TTCAAAGTGG GGATGAAAAG ATCTTCAGTT 1320

AATGGAACAA GAACTAGAGG ATTAGTGTAT TGTTCAAAGC TATAAAATCA AACCAATAGA 1380

TGTATTAAAA AGTGATGTAA CTATCAGACA TTTGGAGAGA GATGGACAAA GGAAAGTGGC 1440

GATAGTGTAA GTTAAATCCT TATCTTTTGT AATGGGGAAT TATTAAAGAT GTTGTAAAGT 1500

CAGTAAGTCA AGAAATTATT GCTCAAACAT ATTATTTAAA GTTAGAAAGT TACCAGACGA 1560

TCTAAAATAA ATATTGTTAA AAGCATTACC TCTAGGGAAT GGGATTTAGA TTTAAAAAGG 1620

GTGGGATGGG AAACTGTGTT TTTCATTTTA AGTCCTTCTG TACTATTTAA TTTTTTACCT 1680

TGTGCATGTA TTACTTTGAA AAAATTTTTA ATAAACCCAA ATAAAAATCT AAAAAAAAAA 1740

AAAAAAAAAA AAAAAAAAAA AAA 1763

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

Met Arg Met Lys Thr Arg Lys Glu Glu Glu Met Gly Ser Ile Lys Gln
1 5 10 15

Trp Thr Leu Leu Arg Met Ser His Ser Arg Val Thr Ala Lys Arg Val
20 25 30

Ser His Pro Arg Val Thr Ala Ile Gln Gln Thr Asn Phe Arg
35 40 45

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 28 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid

(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

CNATCTTAGAG CTCAAAGTTA GGGTCTG 28

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

CNCAGAGCTGT TCTGATACTA AGTCTCAC 29

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

ANACTATCTTC TTCAGAGGCC AGATCACC 29

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CNAGAAGCCAG CTGGCTTTGA ATTTCCTC 29

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CNTTTTCCAAT ATGCTTCAAT GGCTCCGT 29

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

TNGGTAGAAGG AGAGCAGGAA GGCCATGA 29

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

GNCTTCTCTGG CTCAGCCATC TTTTGGGC 29

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

CNGTACACACA AACATACATA AAGAGAGC 29

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

ANACGGACTCT GTCACATAAA CGGTGCTG 29

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 29 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: other nucleic acid
(A) DESCRIPTION: /desc = "oligonucleotide"

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:

GNTGAGATACC CTTTTGGCTG TCACTCTA 29

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 80 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

Met Gln Trp Lys Lys Met Asp Asn Leu Leu Thr Arg Leu Ser Lys Leu
1 5 10 15

Thr Ser Pro Ile Lys Gly Gly Cys Ser Thr Cys Ala Phe Lys Cys Asp
20 25 30

Pro Leu Arg Arg Lys Gln His His Cys Asn Asn Asn Asn Gln Lys Arg
35 40 45

Gln Gly Val Leu Thr Glu Phe Phe Lys Asn Val Asn Val Ile Glu Asp
50 55 60

Lys Glu Arg Leu Trp Lys Cys Phe Arg Leu Asn Asp Ser Lys Asn Thr
65 70 75 80

What is claimed is:

1. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 506 to nucleotide 643;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 471 to nucleotide 765;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AA35_2 deposited under accession number ATCC 98303;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AA35_2 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:2;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:2 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

2. A composition of claim 1 wherein said polynucleotide is operably linked to at least one expression control sequence.

3. A host cell transformed with a composition of claim 2.

4. The host cell of claim 3, wherein said cell is a mammalian cell.

5. A process for producing a protein encoded by a composition of claim 2, which process comprises:

(a) growing a culture of the host cell of claim 3 in a suitable culture medium; and

(b) purifying said protein from the culture.

6. A protein produced according to the process of claim 5.

7. The protein of claim 6 comprising a mature protein.

8. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:2;

(b) the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 32;

(c) fragments of the amino acid sequence of SEQ ID NO:2; and

(d) the amino acid sequence encoded by the cDNA insert of clone AA35_2 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

9. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2.

10. The composition of claim 8, wherein said protein comprises the amino acid sequence of SEQ ID NO:2 from amino acid 1 to amino acid 32.

11. The composition of claim 8, further comprising a pharmaceutically acceptable carrier.

12. A method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of a composition of claim 11.

13. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:1.

14. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 71 to nucleotide 736;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 113 to nucleotide 736;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:3 from nucleotide 1 to nucleotide 343;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone AM42_3 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone AM42_3 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:4;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:4 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

15. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:4;

(b) the amino acid sequence of SEQ ID NO:4 from amino acid 1 to amino acid 91;

(c) fragments of the amino acid sequence of SEQ ID NO:4; and

(d) the amino acid sequence encoded by the cDNA insert of clone AM42_3 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

16. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:3.

17. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:5 from nucleotide 55 to nucleotide 423;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone BG137_7 deposited under accession number ATCC 98303;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone BG137_7 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:6;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:6 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

18. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:6;

(b) the amino acid sequence of SEQ ID NO:6 from amino acid 62 to amino acid 123;

(c) fragments of the amino acid sequence of SEQ ID NO:6; and

(d) the amino acid sequence encoded by the cDNA insert of clone BG137_7 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

19. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:5.

20. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 186 to nucleotide 2030;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 873 to nucleotide 2030;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:7 from nucleotide 802 to nucleotide 1173;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CH699_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CH699_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:8;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:8 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

21. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:8;

(b) the amino acid sequence of SEQ ID NO:8 from amino acid 218 to amino acid 329;

(c) fragments of the amino acid sequence of SEQ ID NO:8; and

(d) the amino acid sequence encoded by the cDNA insert of clone CH699_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

22. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:7.

23. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 111 to nucleotide 677;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:10 from nucleotide 156 to nucleotide 677;

(d) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CO851_1 deposited under accession number ATCC 98303;

(e) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303;

(f) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CO851_1 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:11;

(i) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:11 having biological activity;

(j) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(g) above;

(k) a polynucleotide which encodes a species homologue of the protein of (h) or (i) above ; and

(l) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i).

24. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:11;

(b) the amino acid sequence of SEQ ID NO:11 from amino acid 120 to amino acid 189;

(c) fragments of the amino acid sequence of SEQ ID NO:11; and

(d) the amino acid sequence encoded by the cDNA insert of clone CO851_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

25. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:10, SEQ ID NO:9 or SEQ ID NO:12 .

26. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 123 to nucleotide 755;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 279 to nucleotide 755;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:13 from nucleotide 1 to nucleotide 631;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CP111_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CP111_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:14;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:14 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

27. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:14;

(b) the amino acid sequence of SEQ ID NO:14 from amino acid 1 to amino acid 171;

(c) fragments of the amino acid sequence of SEQ ID NO:14; and

(d) the amino acid sequence encoded by the cDNA insert of clone CP111_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

28. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:13.

29. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 214 to nucleotide 2760;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 406 to nucleotide 2760;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:15 from nucleotide 2011 to nucleotide 2565;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone CS278_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone CS278_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:16;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:16 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

30. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:16;

(b) the amino acid sequence of SEQ ID NO:16 from amino acid 596 to amino acid 784;

(c) fragments of the amino acid sequence of SEQ ID NO:16; and

(d) the amino acid sequence encoded by the cDNA insert of clone CS278_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

31. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:15.

32. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 901 to nucleotide 1074;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 970 to nucleotide 1074;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:17 from nucleotide 626 to nucleotide 1147;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DF968_3 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DF968_3 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:18;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:18 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

33. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:18;

(b) fragments of the amino acid sequence of SEQ ID NO:18; and

(c) the amino acid sequence encoded by the cDNA insert of clone DF968_3 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

34. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:17.

35. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:19 from nucleotide 560 to nucleotide 820;

(c) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DN1120_2 deposited under accession number ATCC 98303;

(d) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303;

(e) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DN1120_2 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303;

(g) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:20;

(h) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:20 having biological activity;

(i) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(f) above;

(j) a polynucleotide which encodes a species homologue of the protein of (g) or (h) above ; and

(k) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(h).

36. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:20;

(b) the amino acid sequence of SEQ ID NO:20 from amino acid 1 to amino acid 61;

(c) fragments of the amino acid sequence of SEQ ID NO:20; and

(d) the amino acid sequence encoded by the cDNA insert of clone DN1120_2 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

37. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:19.

38. A composition comprising an isolated polynucleotide selected from the group consisting of:

(a) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21;

(b) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 649 to nucleotide 786;

(c) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 736 to nucleotide 786;

(d) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:21 from nucleotide 525 to nucleotide 787;

(e) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone DO589_1 deposited under accession number ATCC 98303;

(f) a polynucleotide encoding the full-length protein encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303;

(g) a polynucleotide comprising the nucleotide sequence of the mature protein coding sequence of clone DO589_1 deposited under accession number ATCC 98303;

(h) a polynucleotide encoding the mature protein encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303;

(i) a polynucleotide encoding a protein comprising the amino acid sequence of SEQ ID NO:22;

(j) a polynucleotide encoding a protein comprising a fragment of the amino acid sequence of SEQ ID NO:22 having biological activity;

(k) a polynucleotide which is an allelic variant of a polynucleotide of (a)-(h) above;

(l) a polynucleotide which encodes a species homologue of the protein of (i) or (j) above ; and

(m) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(j).

39. A composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group consisting of:

(a) the amino acid sequence of SEQ ID NO:22;

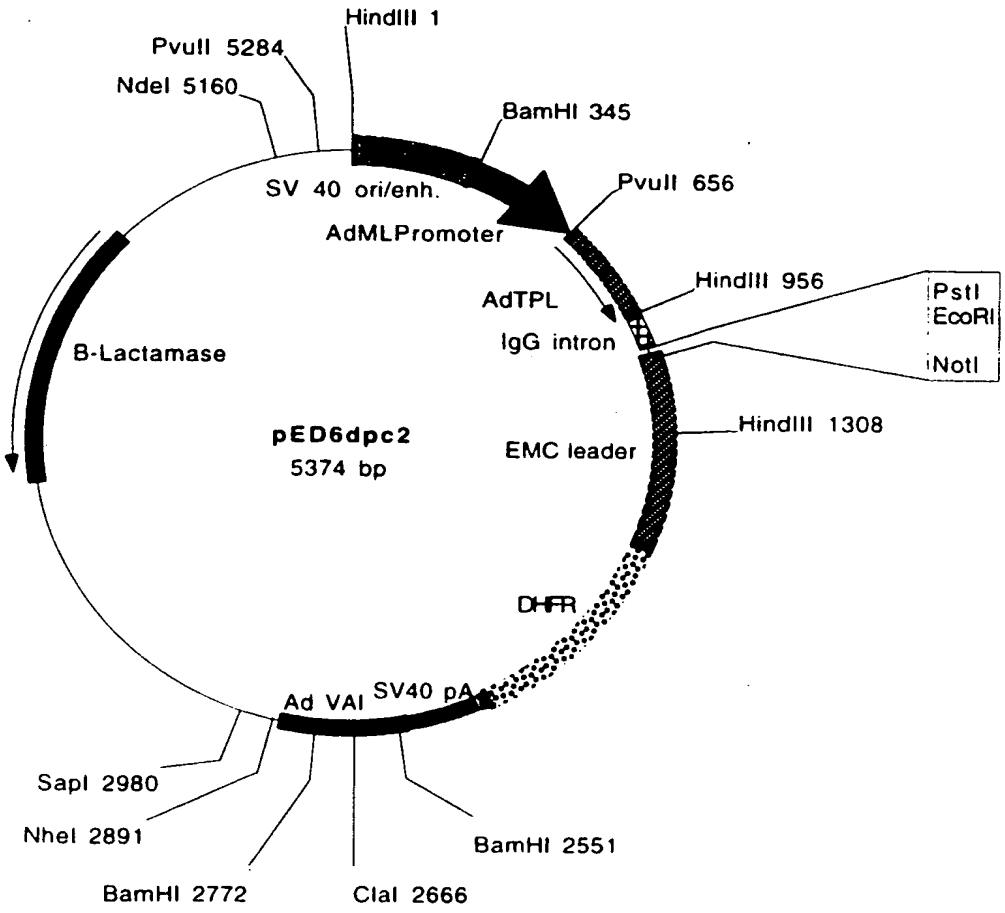
(b) fragments of the amino acid sequence of SEQ ID NO:22; and

(c) the amino acid sequence encoded by the cDNA insert of clone DO589_1 deposited under accession number ATCC 98303;

the protein being substantially free from other mammalian proteins.

40. An isolated gene corresponding to the cDNA sequence of SEQ ID NO:21.

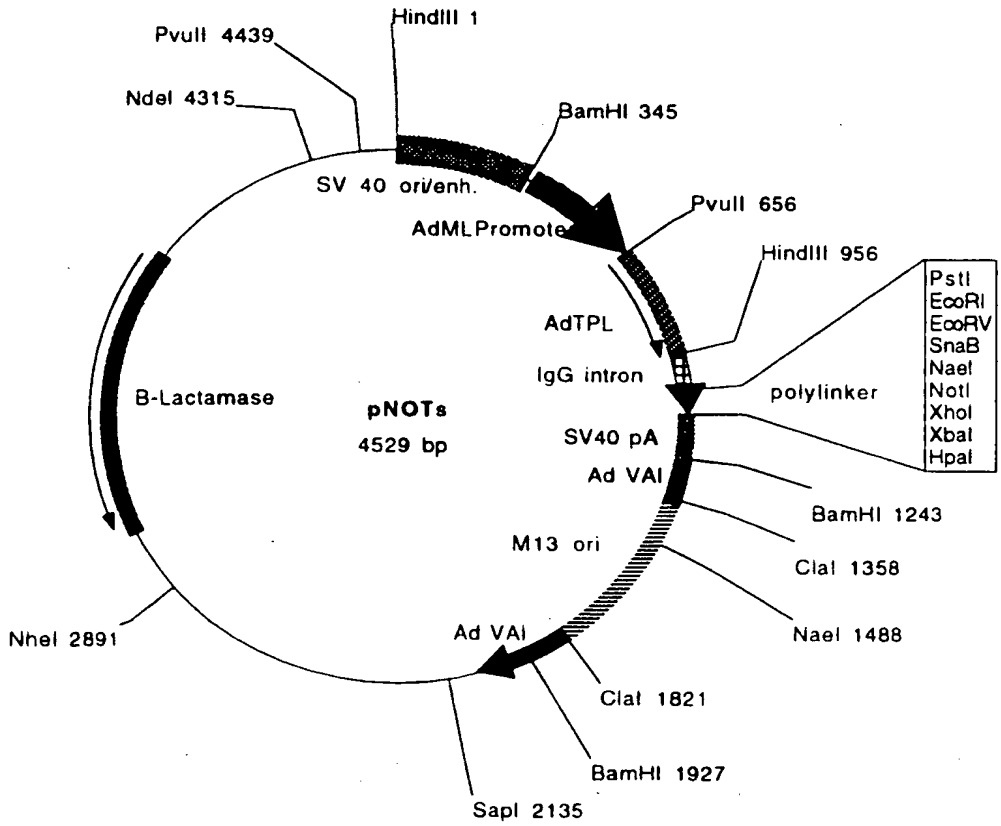
FIGURE 1A



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

FIGURE 1B



Plasmid name: pNOTs
Plasmid size: 4529 bp

Comments/References: pNOTs is a derivative of pMT2 (Kaufman et al,1989. Mol.Cell.Biol.9:1741-1750). DHFR was deleted and a new polylinker was inserted between EcoRI and HpaI. M13 origin of replication was inserted in the ClaI site. SST cDNAs are cloned between EcoRI and NotI

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

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(30) Priority Data:
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(71) Applicant: GENETICS INSTITUTE, INC. [US/US]; 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(72) Inventors: JACOBS, Kenneth; 151 Beaumont Avenue, Newton, MA 02160 (US). MCCOY, John, M.; 56 Howard Street, Reading, MA 01867 (US). LAVALLIE, Edward, R.; 90 Green Meadow Drive, Tewksbury, MA 01876 (US). RACIE, Lisa, A.; 124 School Street, Acton, MA 01720 (US). MERBERG, David; 2 Orchard Drive, Acton, MA 01720 (US). TREACY, Maurice; 93 Walcott Road, Chestnut Hill, MA 02167 (US). SPAULDING, Vikki; 11 Meadowbank Road, Billerica, MA 01821 (US). AGOSTINO, Michael, J.; 26 Wolcott Avenue, Andover, MA 01810 (US).

(74) Agent: SPRUNGER, Suzanne, A.; Genetics Institute, Inc., 87 CambridgePark Drive, Cambridge, MA 02140 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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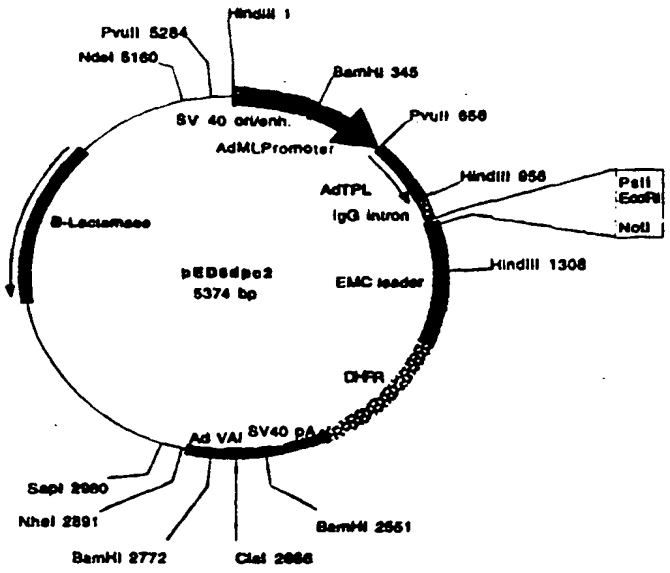
(54) Title: SECRETED PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

(57) Abstract

Polynucleotides and the proteins encoded thereby are disclosed.



Plasmid name: pED6dpc2
Plasmid size: 5374 bp

Comments/References: pED6dpc2 is derived from pED6dpc1 by insertion of a new polylinker to facilitate cDNA cloning. SST cDNAs are cloned between EcoRI and NotI. pED vectors are described in Kaufman et al.(1991), NAR 19: 4485-4490.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 98/01396

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C12N5/10 C07K14/47 C12Q1/68 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K C12Q A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	D. REISMAN ET AL.: "Human unknown protein mRNA within the p53 intron 1, complete cds." EMBL SEQUENCE DATABASE, 28 June 1996, HEIDELBERG,FRG, XP002074811 cited in the application Accession no. U58658 ---	1-13
A	L. HILLIER ET AL.: "The WashU-Merck EST Project" EMBL SEQUENCE DATABASE, 8 July 1995, HEIDELBERG, FRG, XP002074812 cited in the application yn72e01.r1 Homo sapiens cDNA clone 173976 5' similar to contains Alu repetitive element; Accession no. H23653; --- -/--	1-13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 August 1998	17. 11. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	HORNIG H.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ADAMS M D ET AL: "3,400 NEW EXPRESSED SEQUENCE TAGS IDENTIFY DIVERSITY OF TRANSCRIPTS IN HUMAN BRAIN" NATURE GENETICS, vol. 4, no. 3, pages 256-267, XP000611495 see the whole document ---	1-13
A	JACOBS K ET AL: "A NOVEL METHOD FOR ISOLATING EUKARYOTIC CDNA CLONES ENCODING SECRETED PROTEINS" JOURNAL OF CELLULAR BIOCHEMISTRY - SUPPLEMENT, vol. 21A, 10 March 1995, page 19 XP002027246 see abstract ---	1-13
A	EP 0 510 691 A (OSAKA BIOSCIENCE INST) 28 October 1992 see the whole document ---	1-13
A	WO 94 07916 A (MERCK & CO INC ;SCHMIDT AZRIEL (US); RODAN GIDEON A (US); RUTLEDGE) 14 April 1994 see the whole document ---	1-13
A	WO 90 05780 A (OREGON STATE) 31 May 1990 see the whole document ---	1-13
A	WO 90 14432 A (GENETICS INST) 29 November 1990 see the whole document ---	1-13
A	WO 96 17925 A (IMMUNEX CORP) 13 June 1996 see the whole document ---	1-13
A	R.J. KAUFMAN ET AL.: "Effect of von Willebrand factor coexpression on the synthesis and secretion of factor VIII in chinese hamster ovary cells" MOL. CELL. BIOL., vol. 9, no. 3, March 1989, ASM WASHINGTON, DC,US, pages 1233-1242, XP002041592 see the whole document ---	1-13
A	R.J. KAUFMAN ET AL.: "The phosphorylation state of eucaryotic initiation factor 2 alters translation efficiency of specific mRNAs" MOL. CELL. BIOL., vol. 9, no. 3, March 1989, ASM WASHINGTON, DC,US, pages 946-958, XP002041593 see the whole document ---	1-13

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R.J. KAUFMAN ET AL.: "Improved vectors for stable expression of foreign genes in mammalian cells by use of the untranslated leader sequence from EMC virus" NUCLEIC ACIDS RESEARCH, vol. 19, no. 16, 1991, IRL PRESS LIMITED,OXFORD,ENGLAND, pages 4485-4490, XP002041594 cited in the application see the whole document ---	1-13
A	US 5 536 637 A (JACOBS KENNETH) 16 July 1996 cited in the application see the whole document ---	1-13
P,A	WO 97 07198 A (GENETICS INSTITUT) 27 February 1997 see the whole document ---	1-13
P,A	WO 97 25427 A (GENETICS INST) 17 July 1997 see the whole document -----	1-13

INTERNATIONAL SEARCH REPORT

ıtional application No.
PCT/US 98/01396

Box I Obs rvations where rtain claims were found unsearchable (Continuation of it m 1 of first she t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see Further Information sheet enclosed.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1 - 13

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-13

   A composition comprising an isolated polynucleotide selected from the group consisting of: SEQ ID no.1; said composition wherein said polynucleotide is operably linked to an expression control sequence; a host cell transformed with said composition; a process for producing a protein which is encoded by said polynucleotide sequence; a composition comprising a protein, wherein said protein comprises an amino acid sequence selected from the group of SEQ ID no.2, said composition further comprising a pharmaceutical acceptable carrier; a method for preventing, treating or ameliorating a medical condition which comprises administering to a mammalian subject a therapeutically effective amount of said composition, the gene corresponding to the cDNA sequence of SEQ ID no.1;

2. Claims: 14-16

   A composition comprising an isolated polynucleotide sequence selected from the group of SEQ ID no.3; a composition comprises a protein, wherein said protein comprises an amino acid sequence selected from the group of SEQ ID no.4; the gene corresponding to the cDNA sequences of SEQ ID nos.3;

3. Claims: 17-19

   Idem as subject 2 but limited to SEQ ID nos.5 and 6;

4. Claims: 20-22

   Idem as subject 2 but limited to SEQ ID nos.7 and 8;

5. Claims: 23-25

   Idem as subject 2 but limited to SEQ ID nos. 9,10,11 and 12;

6. Claims: 26-28

   Idem as subject 2 but limited to SEQ ID nos.13 and 14;

7. Claims: 29-31

   Idem as subject 2 but limited to SEQ ID nos.15 and 16;

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

8. Claims: 32-34

Idem as subject 2 but limited to SEQ ID nos.17 and 18;

9. Claims: 35-37

Idem as subject 2 but limited to SEQ ID nos.19 and 20;

10. Claims: 38-40

Idem as subject 2 but limited to SEQ ID nos.21 and 22;

REMARK:
Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Inte...nal Application No
PCT/US 98/01396

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